A. M. A.
ARCHIVES OF
SURGERY

EDITORIAL BOARD

WALTMAN WALTERS, Chairman, Rochester, Minn.

LESTER R. DRAGSTEDT, Chicago

ROBERT ELMAN, St. Louis

ALTON OCHSNER, New Orleans

ARTHUR W. ALLEN, Boston

ALFRED BLALOCK, Baltimore

FRANK HINMAN Jr., San Francisco

G. E. LINDSKOG, New Haven, Conn.

BARNES WOODHALL, Durham, N. C.

RICHARD J. PLUNKETT, M.D., Chicago, Managing Editor

MAY 1951

VOLUME 62 NUMBER 5

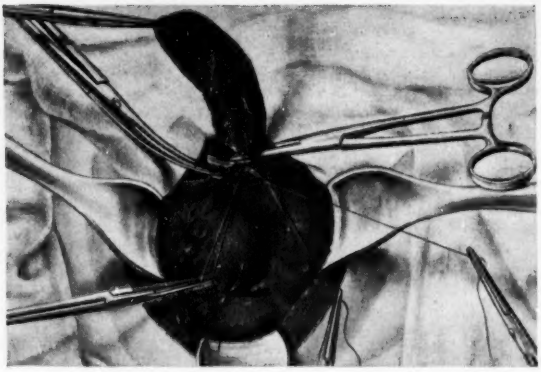
Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter July 10, 1925, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $14.00

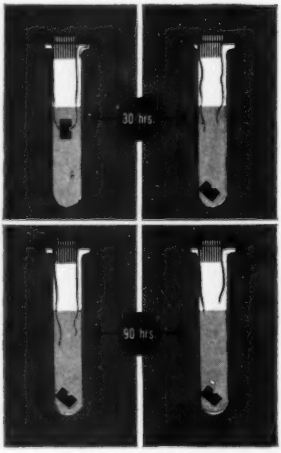
During the critical first 4 days depend on



"TIMED-ABSORPTION" CATGUT

Because "timed-absorption" catgut (surgical gut) has a *measurable* and *predictable* rate of digestion, demonstrated by extensive tests, it remains intact until the wound has gathered support of its own. Because "timed-absorption" catgut does not digest prematurely, it assures strength when needed most – during the critical first 4 days following major surgery.

Processed by an exclusive Davis & Geck method embodying accurately graded degrees of tanning, "timed-absorption" catgut has an absorption curve that parallels the changing tissue conditions of healing. Resistance to digestion is maximal during *early* repair. Later, when artificial strength is no longer required, dissolution is rapid and complete and no remnants of gut remain.



Comparison of D & G "timed-absorption" medium chromic catgut, size 0, with ordinary medium chromic size 0 catgut. Both types of catgut are suspended in a trypsin solution and weighted. Note that at the end of 30 hours D & G "timed-absorption" catgut remains intact; the weight is still held suspended up to 90 hours. Contrast with an ordinary chromic catgut suture which has begun to digest and breaks under the slight tension created by the weight at 30 hours. In human tissue all chromic sutures are digested *more slowly*, but the ratio between the two types remains the same.

D&G catgut sutures have a special matte finish. They tie readily and do not slip at the knot. Pliability is exceptional and tensile strength, diameter for diameter, is guaranteed unexcelled by any other brand. No wonder so many surgeons agree on D&G.

There is a D & G suture for every surgical purpose. Available through responsible dealers everywhere.

DAVIS & GECK, INC.

57 WILLOUGHBY ST., BROOKLYN 1, N. Y.

. . . from Cadiz to Canton

Worldwide reports — Worldwide acceptance
(NOW 1678)

. . . of one anesthetic

Here in the hundreds of reports on PENTOTHAL Sodium is the chronicle of intravenous anesthesia. PENTOTHAL and intravenous anesthesia have grown up together since 1934 when Abbott introduced the ultra-short-acting barbiturate to the medical profession. There is no bulky, frightening apparatus. Induction is rapid, pleasant. The patient has complete surgical amnesia, usually awakens without nausea. Deeper anesthesia may be had in a moment, as the need arises. And PENTOTHAL may be combined with any number of other anesthetics to meet specific, individual requirements. Your medical group may arrange for a showing of a color film, PENTOTHAL in Obstetrics, by writing us, Abbott Laboratories, North Chicago, Illinois. Write, too, for detailed literature on PENTOTHAL. Abbott

As an adjunct to PENTOTHAL Sodium
TUBOCURARINE Chloride, Abbott
. . . supplied in 10-cc. and 20-cc. vials, each cc. representing 3 mg. of tubocurarine chloride pentahydrate. Also 1-cc. ampoules, 15 mg.
Send postcard for literature.

Pentothal® Sodium
(STERILE THIOPENTAL SODIUM, ABBOTT)

for intravenous anesthesia

AND NOW *A New Grip on Problems of Industrial Medicine*

THROUGH A Journal Designed For Your Interests

A. M. A. Archives of INDUSTRIAL HYGIENE and OCCUPATIONAL MEDICINE

Merging the best features of *Occupational Medicine* and *The Journal of Industrial Hygiene and Toxicology.*

Integrated closely with the activities of the Council of Industrial Health of the A. M. A. and the American Industrial Hygiene Association.

Edited by men of outstanding reputation in the fields of industrial health and preventive industrial hygiene: Prof. Philip Drinker, Boston, Chief Editor; Robert Kehoe, M.D., Cincinnati; James Sterner, M.D., Rochester, N. Y.; Frank Patty, Detroit, Mich.; Theodore Hatch, Pittsburgh; Frank Princi, M.D., Cincinnati; Fenn E. Poole, M.D., Glendale, Calif.; William A. Sawyer, Rochester, N. Y.

Covering the research and field aspects of industrial hygiene and the clinical and medical aspects of occupational industrial health programs.

A Better and More Useful Journal of Industrial Medicine!

Such is the result which the Editorial Board of A. M. A. Archives of INDUSTRIAL HYGIENE and OCCUPATIONAL MEDICINE has achieved by combining parallel publications.

To the thousands of physicians who are directly or indirectly concerned today with medicine in industry, the new journal will bring reports of the continuing and important developments in the field, with original articles covering problems and day to day experiences of physicians in industry; an excellent abstracting service similar to that carried in the *Journal of Industrial Hygiene and Toxicology;* additional foreign journal abstracting; reviews.

Whether servicing industrial firms, attending employees, applying to general practice some of the findings of industrial medicine, or merely *watching* this expanding field, you will want to receive this vital new periodical.

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn Street, Chicago 10

Enter my subscription to A. M. A. Archives of INDUSTRIAL HYGIENE and OCCUPATIONAL MEDICINE to start *with the next issue.* Per year, $8.00 in U. S. (Canadian, $8.40; Foreign, $9.00).

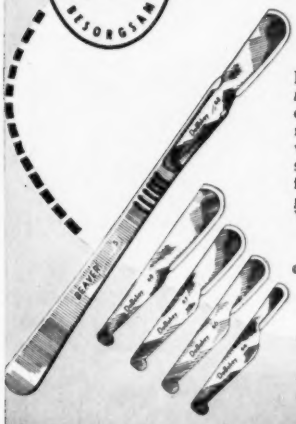
I enclose check..... Please bill me.....

Name.....

Address.....

THE *ONLY* BLADE THAT CUTS CORRECTLY AT...

Any Angle



Because of its unique *all-belly* shape, the Beaver-DeBakey Blade may be used *in any position* — for greater convenience and increased efficiency. It is not a wafer blade — is strong, rigid and *solid* (has no weakening hole); will not weave in an incision, nor break even in orthopedic surgery. Like all other Beaver Blades, this design fits *all* Beaver stainless steel handles. Made and guaranteed by the Rudolph Beaver Company, Waltham 54, Mass., U.S.A.

Only Rudolph Beaver Surgical Knives have completely interchangeable *solid* blades.

SURGICAL KNIVES BY

Ask your dealer or write direct.

Rudolph Beaver

PERRY

Colostomy & Ileostomy Products

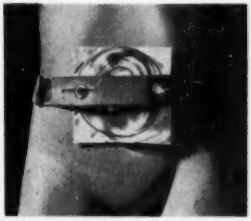
Quality appliances since 1939

Booth No. 33, Annual Session, Am. Proc. Soc., Atlantic City, June 6-9, 1951

Booth No. J 28, Convention of the Am. Med. Assn., Atlantic City, June 11-15, 1951

MODEL 50 ➡

- Can be cemented to the body (optional) and is removable for cleansing without disturbing the cemented portion.
- Connecting disc that cements to body is *flexible*. It conforms to body movements and provides for more successful cementing and greater comfort.
- Can be used with either disposable plastic bags or latex bags.
- Belt can be raised or lowered in ¼" graduations.
- Can be worn with single or double belt.
- Convertible to serve 4 different needs—Colostomy, Ileostomy, Irrigator, or Protector.



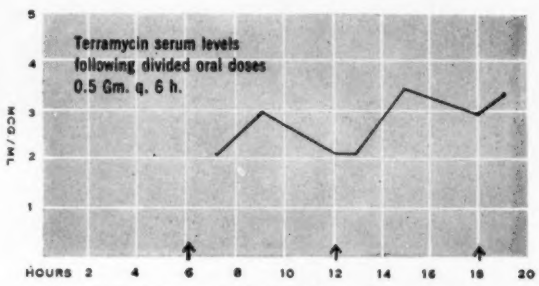
⬅ **PLASTIC CUP** . . . for colostomy patients who do not use the irrigation method, and who do not like the flexible quality of the bag type appliances. ● Contracts no odor ● Easily cleaned ● No replacements ● Sediment bowl below the point of drainage ● Can be worn *under* a girdle or corset.

PERRY appliances are built UP TO A STANDARD not DOWN TO A PRICE. Write for literature.

MURLE PERRY 112 HENNEPIN AVE. MINNEAPOLIS 1, MINN.

in the selection of an antibiotic for surgical infections

rapid contact between pathogen and antibiotic may be a decisive factor



Adapted from Welch, H.: Ann. New York Acad. Sc. 53:253 (Sept. 15) 1950.

CRYSTALLINE

Terramycin

HYDROCHLORIDE

Rapid absorption and distribution following oral administration of Terramycin assures therapeutic serum and tissue levels quickly achieved to halt invasive or spreading infection. Continuous effective levels can be maintained through the administration of 0.5 Gm. q. 6 h. as shown in the accompanying chart.[1]

Terramycin, employed either alone or as an adjunct to surgical procedures, has proved highly satisfactory in the treatment of a wide range of surgical septic conditions such as cellulitis, cellulitis with abscess, infected laceration, human bite infection, furunculosis, carbuncles, abscess, cervical actinomycosis, gas gangrene, and acute hemolytic streptococcal osteomyelitis.[2, 3, 4]

Crystalline Terramycin Hydrochloride is available as *Capsules, Elixir* (formerly Terrabon), *Intravenous, Ophthalmic Ointment* and *Ophthalmic Solution.*

1. Welch, H.: Ann. New York Acad. Sc. 53:253 (Sept. 15) 1950. 2. King, E. Q.; Lewis, C. N.; Welch, H.; Clark, E. A., Jr.; Johnson, J. B.; Lyons, J. B.; Scott, R. B., and Cornely, P. B.: J. A. M. A. 143:1 (May 6) 1950. 3. Pulaski, E. J.: Ann. New York Acad. Sc. 53:347 (Sept. 15) 1950. 4. Herrell, W. E.; Heilman, F. R., and Wellman, W. E.: Ann. New York Acad. Sc. 53:427 (Sept. 15) 1950.

Antibiotic Division **Pfizer** CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

CONTENTS

PAGE

Surgical Implications of Upper Thoracic Independent Sympathetic Pathways. EMERICH EHRLICH JR., M.S., AND WILLIAM F. ALEXANDER, PH.D., ST. LOUIS..... 609

Clinical Significance of the Paraurethral Ducts and Glands. JOHN W. HUFFMAN, M.D., CHICAGO..... 615

Successful Resection of an Angioendothelioma of the Cervical Esophagus: Case Report and Review of the Literature. HAROLD K. PALANKER, M.D.; ANTHONY B. CONSTANTINE, M.D., AND JOHN R. PAINE, M.D., BUFFALO..... 627

Pheochromocytoma: Anesthetic Management During Surgical Treatment. VIRGINIA APGAR, M.D., AND E. M. PAPPER, M.D., NEW YORK..... 634

Effects of Vagus Section with Subtotal Gastrectomy and Diversion of Duodenal Secretions Into the Terminal Portion of the Ileum on Ulcer Development. JAMES V. OLIVER, M.D., CHICAGO..... 649

Effect of Vagotomy and Subtotal Gastric Resection on the Secretion of Mucin in the Human Stomach. GEORGE B. JERZY GLASS, M.D.; WALTER L. MERSHEIMER, M.D., AND CHESTER S. SVIGALS, M.D., NEW YORK..... 658

Observations on the Major Radicles of the Extrahepatic Portal Systems. HARRY K. PURCELL, M.D.; JOHN J. CONNOR, M.D.; WILLIAM F. ALEXANDER, PH.D., AND NIALL M. SCULLY, M.D., ST. LOUIS..... 670

Pain Control Following Upper Abdominal Operations. WALTER H. GERWIG JR., M.D.; CHARLES W. THOMPSON, M.D., AND BRIAN BLADES, M.D., WASHINGTON, D. C. 678

Significance of Postoperative Glycosuria and Ketonuria in Nondiabetic Adults. ROBERT ELMAN, M.D., AND T. E. WEICHSELBAUM, PH.D., WITH THE TECHNICAL ASSISTANCE OF MARJORIE A. GRAUL, R.N., ST. LOUIS..... 683

Coronary Thrombosis and Insufficiency Resulting from Shock: A Clinical and Pathologic Study. HARRY A. DAVIS, M.D.; VINCENT J. PARLANTE, M.D., AND ALVERTA M. HALLSTED, M.D., LOS ANGELES..... 698

Metastatic Versus Primary Carcinoma of the Rectum. HARRY E. BACON, M.D., AND JOHN LAURENS, M.D., PHILADELPHIA..... 705

Total Parotidectomy in Tumors of the Parotid Gland. WILLIAM S. MCCUNE, M.D., WASHINGTON, D. C..... 715

Cerebrovascular Accidents: Surgical Management with Particular Reference to Massive Intracranial Hemorrhage. E. S. GURDJIAN, M.D., AND J. E. WEBSTER, M.D., DETROIT..... 724

THE A. M. A. ARCHIVES OF SURGERY is published by the American Medical Association for the advancement of surgery and as a medium of publication for research, clinical observations and experimental work in surgery.

Manuscripts for publication and correspondence relating to the editorial management, to communications, subscriptions, reprints, etc., should be addressed, A. M. A. ARCHIVES OF SURGERY, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles are accepted for publication on condition that they are contributed solely to the A. M. A. ARCHIVES OF SURGERY. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones will be supplied by the Association when the original illustrations warrant reproduction and when their number is not considered excessive.

Footnotes and bibliographies (the latter are used only in exhaustive reviews of the literature) should conform to the style of the *Quarterly Cumulative Index Medicus*. This requires, in the order given: name of author, title of article and name of periodical, with volume, page, month—day of month if the journal appears weekly—and year.

Matter appearing in the A. M. A. ARCHIVES OF SURGERY is covered by copyright, but as a rule no objection will be made to its reproduction, in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. ARCHIVES OF SURGERY or in any of the other publications issued by the Association will not be permitted.

The A. M. A. ARCHIVES OF SURGERY is issued monthly. The annual subscription price (for two volumes) is as follows: domestic, $14.00; Canadian, $14.40; foreign, $15.50, including postage. Current single copies are $1.25, postpaid, except special numbers.

Checks, money orders and drafts should be made payable to the American Medical Association.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (three volumes): domestic, $15.00; Canadian, $16.50; foreign, $19.00. Single copies, 45 cents.

A. M. A. ARCHIVES OF INTERNAL MEDICINE—Monthly. Devoted to the publication of advanced original clinical and laboratory investigations in internal medicine. Illustrated. Annual subscription price (two volumes): domestic, $10.00; Canadian, $10.40; foreign, $11.00. Single copies, $1.00.

A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. Includes carefully prepared reviews, based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, annual reviews of special subjects, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original articles and general reviews in the field of pathology. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, $1.00, except special issues.

A. M. A. ARCHIVES OF INDUSTRIAL HYGIENE AND OCCUPATIONAL MEDICINE—Monthly. Devoted to the advancement of knowledge of the diseases of industry and to the publication of scientific investigation in this field. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00, including postage. Single copies, $1.00.

QUARTERLY CUMULATIVE INDEX MEDICUS—A complete subject and author index to the worth while current medical literature of the world. Issued twice a year. Volumes bound for permanent reference. Subscription price, calendar year: domestic, $20.00; Canadian, $22.00; foreign, $22.00.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **CHICAGO 10**

A. M. A.
ARCHIVES OF SURGERY

VOLUME 62 MAY 1951 NUMBER 5

COPYRIGHT, 1951, BY THE AMERICAN MEDICAL ASSOCIATION

SURGICAL IMPLICATIONS OF UPPER THORACIC INDEPENDENT SYMPATHETIC PATHWAYS

EMERICH EHRLICH Jr., M.S.
AND
WILLIAM F. ALEXANDER, Ph.D.
ST. LOUIS

ANATOMIC data previously reported from these laboratories [1] support the assumption that accessory ganglions frequently constitute synaptic relay stations in peripheral sympathetic conduction pathways which do not traverse the sympathetic trunk. Such independent sympathetic pathways afford an anatomic explanation for failure to bring about complete sympathetic denervation, particularly of the extremities, by extirpation of the corresponding segments of the sympathetic trunk or section of the preganglionic fibers which reach these segments of the sympathetic trunk through white communicating rami. The results of a detailed study of accessory sympathetic ganglions in the lower thoracic and the lumbar segments in man and their anatomic relationships, reported by Kuntz and Alexander,[2] demonstrate clearly that in many instances the preganglionic fibers which make synaptic contacts in an accessory ganglion reach it directly through the ventral root of the corresponding spinal nerve and that the axons of the ganglion cells with which the synaptic contacts are made in turn extend distalward in the same nerve. Conduction pathways formed in this manner which do not traverse the sympathetic trunk undoubtedly play their part in the sympathetic innervation of the lower extremities. The residual sympathetic nerve activity in the lower extremity frequently observed following extirpation of the thoracolumbar sympathetic trunk can be explained most satisfactorily on the assumption that it is carried out through pathways which do not traverse the sympathetic trunk and which, consequently, are not interrupted by extirpation.

The present study has been undertaken to obtain additional data relative to the occurrence of accessory sympathetic ganglions in the thoracic segments in man, their anatomic relationships to the lower cervical and the thoracic spinal nerves and their significance in the sympathetic innervation of the upper extremity.

From the St. Louis University School of Medicine.

This work has been aided by a grant from the division of research grants and fellowships of the National Institutes of Health, United States Public Health Service.

1. Alexander, W. F.; Kuntz, A.; Henderson, W. P., and Ehrlich, E., Jr.: Sympathetic Conduction Pathways Independent of Sympathetic Trunks—Their Surgical Implications, J. Internat. Coll. Surgeons **12**:111-119 (March-April) 1949.

2. Kuntz, A., and Alexander, W. F.: Surgical Implications of Lower Thoracic and Lumbar Independent Sympathetic Pathways, Arch. Surg. **61**:1007-1018 (Dec.) 1950.

MATERIAL AND METHODS

The thoracic spinal nerves from the first to the tenth inclusive, their interconnecting rami and the rami through which they are connected with the sympathetic trunk have been studied in detail in a series of human dissections. The thoracic spinal nerves, their proximal rami, including the interconnecting and the communicating rami, and the sympathetic trunks were carefully mapped bilaterally. The proximal portion of every thoracic spinal nerve dissected and its proximal rami were then removed and prepared for histologic study. The corresponding portions of upper thoracic nerves have also been obtained at autopsy and prepared for histologic study by the Nonidez silver technic. The histologic preparations were studied to discover accessory ganglions which could not be observed macroscopically and to determine the morphologic characters of the ganglion cells and the anatomic relationships of the accessory ganglions to the primary rami of the spinal nerves and to the interconnecting and the communicating rami. To facilitate the study of the relationships of the preganglionic and the postganglionic fibers, the embedded tissues were oriented for sectioning so that the spinal nerves were cut longitudinally and the sympathetic trunk was cut transversely. The sections were mounted serially. Except for the fresh material which was prepared by the silver technic of Nonidez, the sections were stained with hematoxylin and eosin. The proximal portions of the spinal nerves with their interconnecting and communicating rami in 73 thoracic segments were studied in serial sections.

ANATOMIC DATA

Accessory sympathetic ganglions were observed in 63 per cent of the segments examined. Most of them comprised only small groups of ganglion cells. The largest ones observed were located in relation to the primary ventral rami of second thoracic nerves. In at least one instance an accessory ganglion associated with the second thoracic nerve could be observed macroscopically. It comprised several thousand ganglion cells.

Most of the accessory sympathetic ganglions in the thoracic segments are located in relation to white communicating rami and sympathetic roots. Occasional ones occur in rami which interconnect adjacent spinal nerves. In one instance an aggregate of sympathetic ganglion cells was observed in the ramus of the first thoracic nerve which joins the brachial plexus. Occasionally groups of ganglion cells were also observed in rami other than sympathetic roots which arise from the sympathetic trunk.

Accessory sympathetic ganglion cells which are embedded in spinal nerves or which are located adjacent to primary ventral rami and those which are located in white communicating rami undoubtedly represent nerve cells which, in their displacement from the neural tube during embryonic development, failed to reach the sympathetic trunk. As indicated by the observations made on the serial sections of the nerves studied in this investigation, these ganglion cells become synaptically related to preganglionic fibers which reach them directly through the corresponding ventral nerve root. Their axons in turn extend distalward in the nerve trunk and its peripheral branches. Conduction pathways are built up in this manner which do not traverse the sympathetic trunk. The relationships of such pathways and the synaptic contacts involved, as indicated by a study of the serial sections of a second thoracic nerve and the tissues adjacent to it, are illustrated diagrammatically in figure 1. This ganglion lies adjacent to the primary ventral ramus of the nerve and in relation to the white communicating ramus. It receives preganglionic fibers chiefly, perhaps exclusively, through the ventral root of the second thoracic nerve. Most of the postganglionic fibers which arise in it extend distalward in this nerve. Some probably join the sympathetic trunk. Still others apparently join neither the

second thoracic nerve nor the sympathetic trunk. A small ganglion embedded in a slender ramus arising from this nerve also receives preganglionic fibers via the ventral nerve root. Postganglionic fibers arising in it traverse the ramus into an adjacent segment.

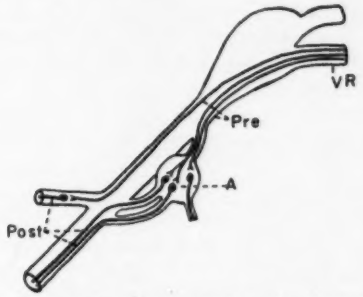


Fig. 1.—Diagrammatic representation of sympathetic conduction pathways with synaptic connections in accessory ganglions located in relation to a second thoracic nerve, based on a study of serial sections of the nerve and adjacent tissues. *A*, accessory ganglions; *Pre*, preganglionic fibers; *Post*, postganglionic fibers; *VR*, ventral nerve root.

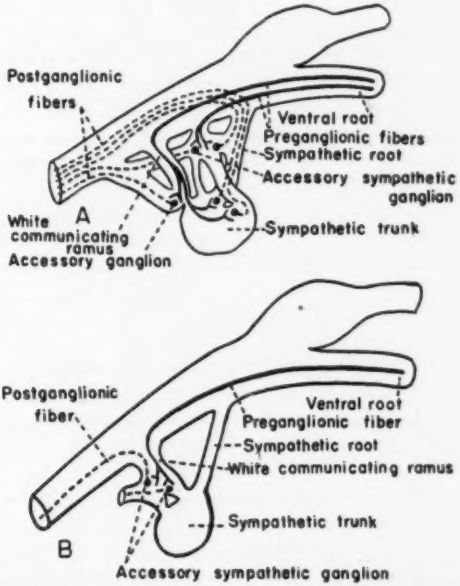


Fig. 2—Diagrammatic representations of connections of sympathetic trunk with spinal nerves as observed in dissections, locations of accessory ganglions as observed in sections, and probable conduction pathways which do not traverse the sympathetic trunk. *A*, from a third thoracic segment; *B*, from a fourth thoracic segment.

The postganglionic fibers which arise in accessory sympathetic ganglions located adjacent to spinal nerves in most instances extend distalward in the spinal nerves. In some instances slender rami which join neither a spinal nerve nor the sym-

pathetic trunk could be traced from such ganglions. They probably convey postganglionic fibers directly to visceral organs.

The axon of a ganglion cell located in the proximal portion of a white communicating ramus may extend distalward in the spinal nerve without passing through the sympathetic trunk, as illustrated in figure 2, or it may extend into the sympathetic trunk and emerge through a sympathetic root. Accessory sympathetic ganglion cells located in a sympathetic root or another ramus arising from the sympathetic trunk undoubtedly represent nerve cells which have been displaced from the sympathetic trunk. They are synaptically related to preganglionic fibers which reach them through the sympathetic trunk. The conduction pathways of

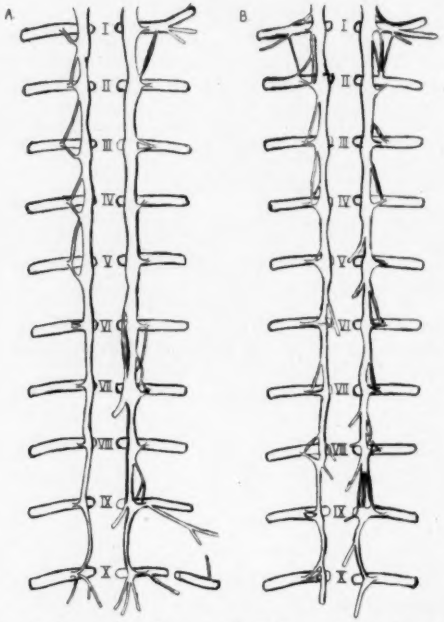


Fig. 3.—Diagrams based on dissections to illustrate variations in the connections of the sympathetic trunks with the thoracic nerves, rami interconnecting adjacent spinal nerves and rami interconnecting a spinal nerve and a sympathetic trunk ganglion in an adjacent segment.

which these ganglion cells constitute the distal links obviously traverse the sympathetic trunk.

The white communicating rami and the sympathetic roots of the thoracic nerves vary in their anatomic relationships both to the spinal nerves and to the sympathetic trunk. The variations are most abundant in the rostral four thoracic segments. No general patterns of variation could be recognized. Neither are these rami symmetrical on the two sides. The arrangements of the connections of the sympathetic trunks with the spinal nerves as observed in certain bodies are illustrated in figure 3.

A ramus which arises from the second thoracic nerve near the junction of the sympathetic root with the nerve trunk and joins the first thoracic nerve proximal

to the origin of the ramus which joins the brachial plexus was observed in most of the bodies examined (fig. 3). A similar ramus arising from the third thoracic nerve and joining the second nerve was observed in a somewhat lesser percentage of the bodies examined. These rami, as has been pointed out by Kuntz [3] and by Kirgis and Kuntz,[4] convey both sympathetic and somatic fibers. They obviously constitute pathways through which postganglionic fibers arising in the second, third and lower thoracic sympathetic trunk ganglions may enter the brachial plexus without traversing the upper thoracic portion of the sympathetic trunk.

In certain of the bodies examined the fourth and third thoracic nerves also were interconnected by a slender ramus the course of which was approximately parallel to that of the sympathetic trunk. This ramus, like the interconnecting rami in the more rostral thoracic segments, probably also conveys both sympathetic and somatic fibers. In some instances an intersegmental ramus was observed to connect the white communicating ramus or the spinal nerve in one segment with the sympathetic trunk ganglion in an adjacent segment. A ramus arising from a sympathetic trunk ganglion may also join the spinal nerve in the next more rostral segment (fig. 3).

SURGICAL IMPLICATIONS

Residual sympathetic nerve activity in the upper extremity following cervicothoracic sympathetic trunk extirpation has been reported so frequently that its occurrence in the absence of any sympathetic conduction pathways with synaptic connections in the sympathetic trunk cannot be denied. The anatomic data obtained in the present investigation confirm the frequent occurrence of accessory sympathetic ganglions, particularly in the rostral two or three thoracic segments. As has been pointed out, the cells in the accessory ganglions which are located in relation to the ventral primary rami of the spinal nerves are synaptically related to preganglionic fibers which reach them through the corresponding ventral nerve roots. Their axons in turn extend distalward in the spinal nerves with which the ganglions are associated. Thus sympathetic conduction pathways which do not traverse the sympathetic trunk are conveyed into the upper extremity. Such independent sympathetic pathways, as indicated by the relatively large numbers of accessory sympathetic ganglion cells in the rostral thoracic segments in some of the bodies studied, are sufficiently abundant in the upper extremity in many instances to account for extensive sympathetic nerve activity following extirpation of the cervicothoracic sympathetic trunk. It is pertinent, therefore, to consider possible surgical procedures which will insure interruption of the independent sympathetic conduction pathways as well as those with synaptic connection in the sympathetic trunk.

Smithwick [5] has described an operative procedure in which both roots of the second and third thoracic nerves are severed and a segment of each nerve, including the site of origin of the white communicating ramus, is removed. This procedure

3. Kuntz, A.: Distribution of the Sympathetic Rami to the Brachial Plexus: Its Relation to Sympathectomy Affecting the Upper Extremity, Arch. Surg. **15**:871-877 (Dec.) 1927.

4. Kirgis, H. D., and Kuntz, A.: Inconstant Sympathetic Neural Pathways: Their Relation to Sympathetic Denervation of the Upper Extremity, Arch. Surg. **44**:95-102 (Jan.) 1942.

5. Smithwick, R. H.: The Problem of Producing Complete and Lasting Sympathetic Denervation of the Upper Extremity by Preganglionic Section, Ann. Surg. **112**:1085-1100 (Dec.) 1940.

results not only in interruption of the preganglionic fibers in the second and third thoracic nerves but also in the removal of any accessary ganglion cells which may be associated with these nerves. In conjunction with cervicothoracic sympathetic trunk extirpation and interruption of the interconnecting rami between the adjacent upper thoracic nerves, if such rami are present, it probably would insure complete sympathetic denervation of the upper extremity in most cases. In cases in which there are accessory sympathetic ganglion cells associated with the first thoracic nerve, the independent conduction pathways of which they constitute the distal links would remain intact. Interruption of these pathways would necessitate section of the ventral root of the first thoracic nerve. This, however, would result in extensive motor defects, whereas the motor and the sensory defects caused by section of the roots of the second and third thoracic nerves are relatively slight.

In general, probably only a relatively small percentage of the preganglionic fibers of the first thoracic nerve which make synaptic contacts in the sympathetic trunk are concerned with the sympathetic innervation of the upper extremity. Sympathetic pathways which do not traverse the sympathetic trunk but which comprise preganglionic fibers of the first thoracic nerve probably are distributed chiefly in the upper extremity. As indicated by the data obtained in the present study, however, accessory sympathetic ganglions which are associated with the spinal nerves appear to occur less frequently in the first thoracic than in the second thoracic segment.

SUMMARY

The frequency of occurence and the anatomic relationships of accessory sympathetic ganglions in the thoracic segments from the first to the tenth inclusive have been studied in a series of dissections and in neurohistologic preparations. Accessory ganglions occur more frequently in the four rostral thoracic segments than in the fifth to the tenth segment. Some are embedded in the spinal nerves or lie immediately adjacent to them near the origins of the white communicating rami. Most of them are located in relation to communicating rami. Most of the accessory ganglion cells, except those associated with gray communicating rami or sympathetic roots, are synaptically related to preganglionic fibers which reach them directly through the ventral nerve roots. Their axons in turn extend distalward in somatic rami of the spinal nerves and possibly in some small visceral rami. Sympathetic conduction pathways are formed in this manner which do not traverse the sympathetic trunk.

The sympathetic pathways which are independent of the sympathetic trunk are not interrupted by extirpation of the sympathetic trunk. Their interruption necessitates section of the nerve roots which convey the preganglionic fibers concerned. Section of the roots of the second and third thoracic nerves causes relatively little sensory and motor paralysis. Section of the ventral root of the first thoracic nerve results in considerable motor defect. Accessory sympathetic ganglions probably occur less frequently in the first thoracic segment than in the second and third segments. Except in cases in which there are accessory ganglion cells associated with the first thoracic nerve, resection of the roots of the second and third thoracic nerves, in conjunction with extirpation of the cerviothoracic sympathetic trunk and interruption of the intersegmental rami in the upper thoracic segments, if such rami are present, probably would insure complete sympathetic denervation of the upper extremity.

CLINICAL SIGNIFICANCE OF THE PARAURETHRAL DUCTS AND GLANDS

JOHN W. HUFFMAN, M.D.
CHICAGO

THE DETAILED anatomy of the paraurethral ducts and glands has been described in a previous contribution.[1] At that time it was shown by serial section wax model reconstructions that the normal female urethra is surrounded by a labyrinthine mass of paraurethral tubules, canaliculi and glandular elements. These structures are homologs of the prostate.[2] While they are vestigial in the female, they may at times give rise to pathologic entities of clinical significance.

Historically, it is of interest to note that Regeneri de Graaf described [3] and illustrated (fig. 1) a glandlike structure about the female urethra which he called a female prostate. Alexander Skene [4] drew attention to two paraurethral ducts (Skene's ducts) and emphasized their importance in infections of the female genitalia. Skene's contribution was based on anatomic studies, and the illustrations (fig. 2) accompanying it are still the basis for most of the descriptions in modern textbooks.

For some time after Skene's presentation, the concept was accepted that there were two paraurethral tubules (Skene's ducts) with occasional lesser urethral lacunas or crypts; the latter were considered to be of little clinical significance. In recent years, however, interest in the subject reawakened, and a lively debate has taken place as to the presence or absence of other urethral ducts and glands. An attempt to reconcile divergent views on the matter resulted in the aforementioned study of the detailed anatomy of the paraurethral structures. Three dimensional wax model reconstructions created from serial sections of adult urethras were made; with these it was possible to demonstrate the extent and architecture of the paraurethral ducts and glands.

ANATOMY AND PHYSIOLOGY

It is now possible to state definitely that there are numerous (rather than two, as described by Skene) ducts and epithelial-lined pockets which empty into the distal third of the female urethra. These ducts and their terminal divisions produce

From the Department of Obstetrics and Gynecology, Northwestern University Medical School and the Obstetrical and Gynecological Service of Passavant Memorial Hospital.

1. Huffman, J. W.: The Detailed Anatomy of the Paraurethral Ducts in the Adult Human Female, Am. J. Obst. & Gynec. **55**:86, 1948.

2. Johnson, F. P.: Homologue of Prostate in Female, J. Urol. **8**:13, 1922. Huffman, J. W.: Development of Periurethral Glands in the Human Female, Am. J. Obst. & Gynec. **46**:773, 1943.

3. de Graaf, R.: De mulerium organis generationi inserventibus tractatus novus, demonstrans tam homines et animalia caetera omnia, quae vivipara dicuntur, haud minus quam ovipara ab ovo originem ducere, Leyden, 1672, p. 66.

4. Skene, A. J. C.: The Anatomy and Pathology of 2 Important Glands of the Female Urethra, Am. J. Obst. **13**:265, 1880.

a widespread branching of tubular channels and glands which surround the female urethra to some extent on all sides, mostly laterally and posteriorly (fig. 3). They tend to be arranged in four groups, with a ventrolateral group and a posterolateral group on each side. In addition to these larger groups there are often a number of ducts opening into the lateral, the dorsal and occasionally the ventral urethral walls. The number of ducts varies greatly in different specimens, i. e., from six to 31. They usually do not surround the entire length of the urethra; commonly they are limited to the distal half. The terminal branches of some of the larger ducts frequently extend cephalad for a considerable distance parallel to the urethral canal and may reach to within a few millimeters of the bladder. Sections through the

Fig. 1.—Photograph (retouched) of illustration in de Graaf's "De mulerium organis generatoni inserventibus," published in 1672. The bladder (*A*) has been opened. Two "prostatic ducts" (*EE*) are shown in the substance of the "female prostate" (*GG*), surrounding the urethra (*C*). The shapes of the ducts and their branches are shown in *FF*.

middle and proximal urethra show a widespread dissemination of ducts, terminal tubules and glands forming a labyrinthine mass which spreads ventrolaterally and ventral to the urethral canal or surrounds it on all sides. The paraurethral ducts terminate in branched tubular glands which are lined for the most part by columnar epithelium. There are occasional nests of mucus-secreting cells within this columnar epithelium.

Two larger paraurethral ducts as described by Skene were noted in some but not all of the specimens which were used in the preparation of the wax model reconstructions. When they were found, their structure was identical with that of the

other paraurethral tubules. It can be assumed that while paraurethral ducts and glands normally occur in the human female, two large tubules are not always present. "Skene's ducts" are paraurethral ducts and are distinguished from the other paraurethral ducts only by their size and location.

Relatively few large paraurethral ducts open into the proximal urethra. There are, however, frequent crypts and lacunas in the proximal urethral mucosa which

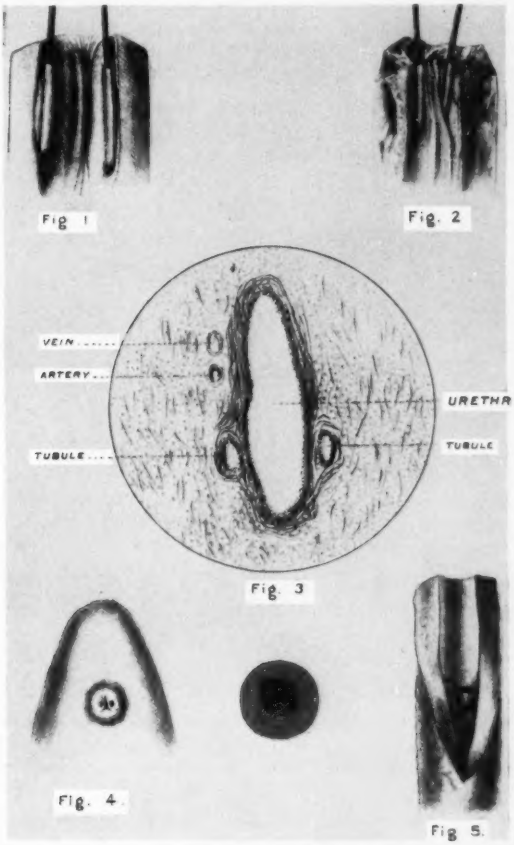


Fig. 2.—Photograph of illustration accompanying Skene's original article describing "Skene's ducts" *(Am. J. Obst.* **13**:265, 1880). In *1* and *2* the urethra has been sectioned longitudinally and probes inserted in the ducts; *3* is a transverse section through the urethra one fourth of an inch (0.64 cm.) within the meatus, *4* demonstrates the orifices of the ducts at the meatus and *5* shows the branches of a duct as seen when the duct is opened longitudinally.

are lined by the same type of epithelium as that which lines the terminal paraurethral glands and tubules. Apparently these invaginations of the posterior urethra arise from the same embryonic source as the larger structures found in the distal urethra.

Since only a portion of the epithelium lining the paraurethral ducts and glands shows evidence of secretory activity, it is doubtful if these vestigial remnants have any appreciable function. Kelly's suggestion that such secretion as is elaborated serves to lubricate the urethral mucosa seems to be a tenable hypothesis. It has also been suggested that sexual stimulation causes the paraurethral glands to elaborate a mucoid secretion comparable to that produced by the glands of the male urethra.

CLINICAL ASPECTS

The urologic aspects of urethral examination, particularly urethroscopy, are beyond the scope of this presentation. However, certain details of examination

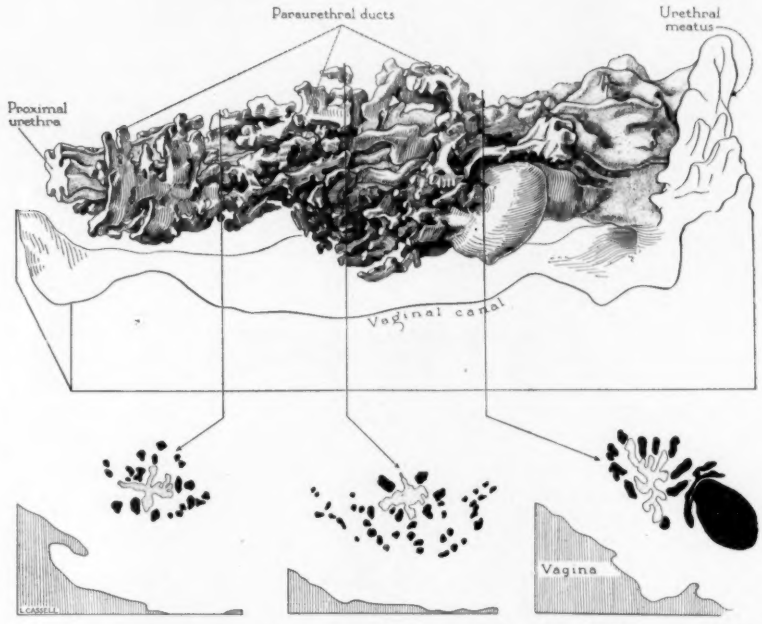


Fig. 3.—Drawing of wax model of an adult human female urethra with its paraurethral glands and ducts as seen in right lateral view. The smaller diagrams demonstrate transverse sections through the urethra, the paraurethral ducts and glands and the vagina beneath the urethra at different levels above the meatus. The model represents the distal 2.4 cm. of a urethra which had a total length of 2.8 cm. (Huffman, *Am. J. Obst. & Gynec.* **55**:86, 1948.)

which are helpful in detecting lesions of paraurethral duct or gland origin merit mention. With the patient in the usual lithotomy position and the vulvar labia well separated, light digital pressure near the urethral meatus will cause the urethral labia to fall apart, exposing the orifices of the outermost paraurethral ducts (fig. 4). When so exposed, they may be aspirated by a finely pointed eye dropper. Gentle pressure exerted transversely on the anterior vaginal wall beneath the outer third of the urethra may reveal inflammatory induration or thickening along the course of the posterolateral ducts; induration of this type is pathognomonic of a previous

neisserian infection. Pressure from within outward along the urethra may express purulent material from the ducts, in a manner analogous to obtaining prostatic secretion in the male. Digital pressure on the anterior vaginal wall beneath the urethra will discover tumefactions in the urethrovaginal septum. A gush of seropurulent material from the meatus when pressure is made on an anterior vaginal wall tumor is strongly suggestive of a urethral diverticulum.

Most lesions of the urethrovaginal septum of paraurethral origin can be detected during a routine vaginal examination. There are, however, some lesions in the anterior vaginal wall which cannot be satisfactorily visualized in the lithotomy posi-

Fig. 4.—When the urethral labia are separated, the openings of the larger paraurethral ducts may frequently be seen as pitlike depressions just within the meatus.

tion. In these cases, recourse to the Sims position and use of a Sims speculum will be found most helpful in exposing the anterior vaginal wall.

LESIONS OF PARAURETHRAL ORIGIN

Infections of the Paraurethral Ducts and Glands.—Concomitant infection of the paraurethral ducts invariably accompanies acute gonorrheal urethritis and may persist as an undiscovered source of reinfection during the later stages of the disease. As Everett points out, chronic infections in the paraurethral glands and ducts as sequelae of gonorrheal urethritis are seldom seen since the advent of modern chemotherapeutic and antibiotic agents for treating gonorrhea. Recurrent or chronic neisserian infections often produce bristle-like thickening of the posterolateral para-

urethral ducts. This thickening is best noted as an examining finger in the vagina is passed transversely beneath the urethra near the meatus.

Paraurethral ducts and glands play an important role in nonspecific urethritis. They act as a nidus for many chronic infections of the female urethra. In such cases stripping of the urethra by outward pressure along the anterior vaginal wall will result in the expression of several drops of purulent material from the ducts. In chronic cases of long duration or in cases in which there have been repeated or traumatic catheterizations inflammatory thickening of the periurethral tissues may

Fig. 5.—Inflammatory reaction about a paraurethral duct with abscess formation and destruction of duct epithelium.

develop. Such periurethritis may simulate a neoplasm. Histologic sections of the female urethras frequently show marked inflammatory reactions about the paraurethral ducts (fig. 5), sometimes with destruction of the duct epithelium and occasionally with true abscess formation.

The paraurethral ducts may at times harbor Trichomonas vaginalis. In recurrent or intractable vaginal trichomoniasis, examination of material aspirated from the paraurethral ducts may reveal trichomonads, thereby explaining one factor in persistent reinfestations of the vagina.

Suburethral Abscess.—The paraurethral glands and ducts are frequently the sites of small abscesses from which a few drops of purulent material can be expressed. Less frequently a larger abscess resulting from obstruction of the narrow outlet of an infected paraurethral duct may extend along the fascial planes between the urethra and the vagina (fig. 6). Abscesses forming within the ducts may eventually rupture into the urethra and, as the result of repeated infections, obstructions and poor drainage, enlarge sufficiently to become urethral diverticula. In rare cases a suburethral abscess will rupture into the vagina, with the formation of a chronically draining sinus in the urethrovaginal tissues.

Cysts of the Paraurethral Duct.—Cystic dilatation of one of the paraurethral ducts is common and is frequently seen in histologic preparations of urethras and urethrovaginal septums. These small, at times microscopic, retention cysts are usually connected to a duct or to the urethra by a narrow strand of epithelium (fig. 7). Larger retention cysts of the paraurethral ducts occasionally produce tumefactions of the anterior vaginal wall and the suburethral tissues (fig. 8). Typically such tumors are seldom more than 2 or 3 cm. in diameter, are not large enough to concern the patient and are of importance only because of their relation to urethral diverticula. They may in rare instances cause dyspareunia.

Anterior or anterolateral vaginal wall cysts may be of mesonephric (Gartner) duct origin or of paramesonephric (Müllerian) origin, inclusion cysts from buried fragments of vaginal mucosa, or they may arise in an obstructed paraurethral duct. While mesonephric and paramesonephric cysts are characteristically in the lateral or anterolateral vaginal wall, paraurethral duct cysts are typically located in the midline. Histologically the latter tumors are usually lined by a low cuboidal (fig. 9) or pseudostratified columnar epithelium similar to that which lines the terminal portions of the paraurethral ducts.

Neoplasms of Paraurethral Origin.—Neoplasms with glandular constituents of the female urethra are comparatively rare. Although caruncles occasionally contain paraurethral glands, inflammations of the paraurethral ducts and glands are not a factor in the development of caruncles. Most often the typical caruncle is of an angiomatous character and is devoid of glandular elements. The possibility that adenocarcinoma of the female urethra may arise from caruncles has been mentioned in the literature. When it does, the adenocarcinoma can best be explained as beginning in the paraurethral glandular tissue incorporated in the caruncle. Walther,[5] in commenting on caruncles, has wisely voiced a warning against removal of proliferative lesions of the female urethra without submitting them to microscopic study.

Adenomas of the female urethra are infrequent. They have been described as painless, mobile, well localized, symptomless nodules located within the urethral meatus. Histologically they are composed of a stroma of connective tissue surrounding simple tubular glands, unstriated muscle fibers and blood vessels. The glandular elements described have the same histologic appearance and architectural form as the paraurethral ducts and glands and are presumably of paraurethral origin. Adenomas of the female urethra may undergo malignant change with the formation of adenocarcinoma.

It is generally accepted that adenocarcinoma of the female urethra originates in the paraurethral glands. When it is realized that the paraurethral structures are

5. Walther, H. W. E.: Caruncle of the Urethra in the Female with Special Reference to Importance of Histological Examination in Differential Diagnosis, J. Urol. **50**:380, 1943.

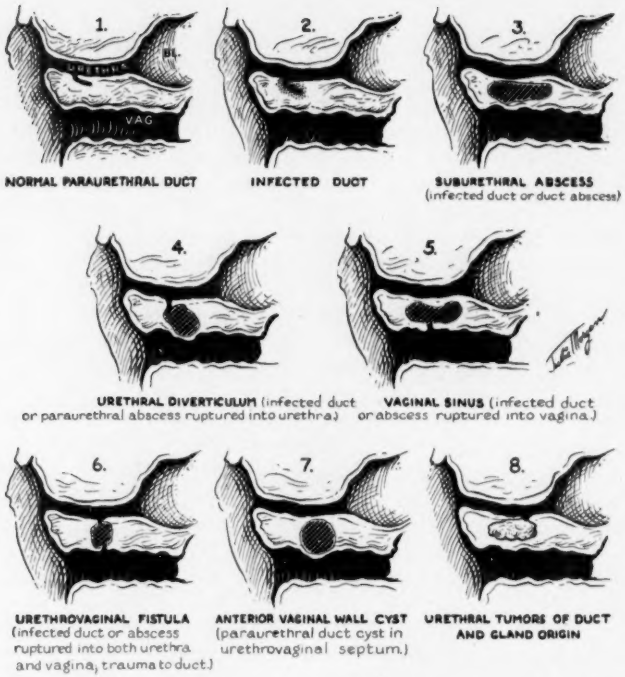


Fig. 6.—Diagrammatic drawing illustrating possible pathologic entities which may develop from a paraurethral duct.

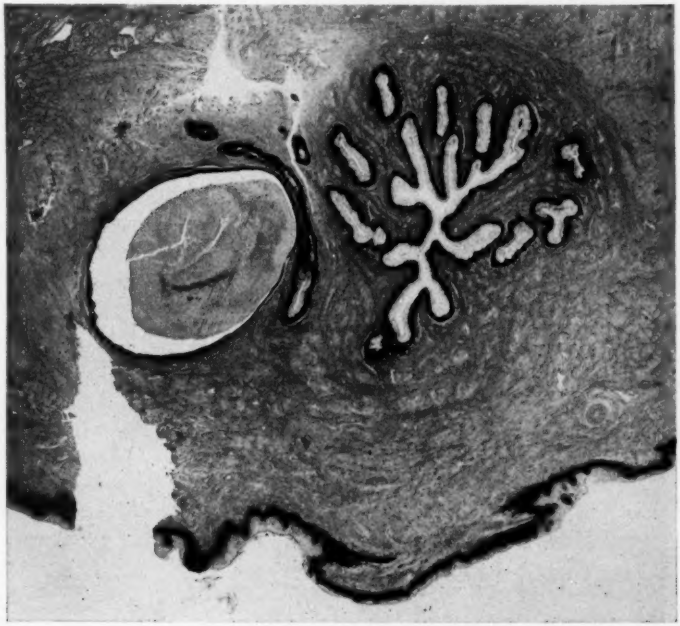


Fig. 7.—Retention cyst of a paraurethral duct. Photomicrograph of a section through the urethra and the periurethral tissues. The defect in the vaginal mucosa is an artefact.

extensive ramifications of epithelial cell-lined tubules containing intraepithelial mucus-secreting glands and terminating in true tubular glands, it is understandable that adenocarcinoma may develop in them. Whitehouse [6] and Graves and Guiss [7]

Fig. 8.—Paraurethral duct cyst of anterior vaginal wall. This tumefaction was a smooth, firm mass 2.0 cm. in diameter situated between the vaginal mucosa and the middle third of the urethra.

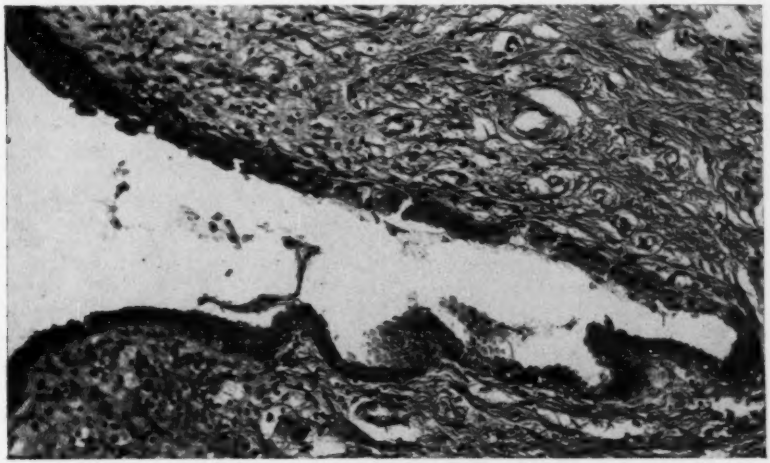


Fig. 9.—Photomicrograph of the lining of a paraurethral duct cyst. Low columnar or pseudostratified columnar epithelium may fuse into transitional epithelium such as is found in the urethra. (Courtesy of Dr. Cary M. Dougherty.)

6. Whitehouse, B.: Primary Carcinoma of the Female Urethra, J. Obst. & Gynaec. Brit. Emp. **20**:269, 1911.

7. Graves, R. C., and Guiss, L. W.: Tumors of the Urethra, J. Urol. **46**:925, 1941.

have pointed out the similarity between adenocarcinoma of the female urethra and prostatic carcinoma. The disease is rare and is usually one of later life. On the basis of available case reports,[8] the neoplasm may appear as an ovoid or polypoid dark red mass arising from the floor of the urethra and protruding from the meatus or, as described by Boyd,[9] Battle [10] and McMurty,[11] it may be a slowly developing collar-like growth in the deeper periurethral tissues, completely surrounding the urethra without early ulceration of the mucosa. Menville [12] has emphasized the fact that the commonest place for the first appearance of all types of carcinoma of the female urethra is immediately within the meatus and observed that it is at this level that the mouths of the paraurethral ducts are particularly prone to irritation and infection. These tumors characteristically consist of simple tubular glands, usually dilated, set into a matrix of blood vessels, unstriated muscle and connective tissue. The tubules are usually lined by columnar epithelium of several layers and have the cytological characteristics of a malignant process (fig. 10). The glandular epithelium may be found breaking through the basement membrane and descending by irregular columns into the surrounding tissue.

Diverticula of the Urethra.—There is a lack of unanimity of opinion not only as to what constitutes diverticula of the female urethra but also on the question of their etiology. Sir Charles Masefield [13] first described such clinical entities in 1814, and Bozeman [14] published the first account in America in 1871. Young and McCrea [15] appropriately described a urethral diverticulum as "a fluid filled pouch located at or immediately above the vaginal introitus which is in direct communication with the urethra as shown by the extrusion of pus and urine from the urinary meatus when pressure is applied to the pouch." They note that objection to the use of the term "diverticulum" has been made by those who examine tissues histologically on the basis that the wall of the diverticular sac is composed of inflammatory tissue rather than mucosa, submucosa and a muscular coat. No matter what descriptive term is used, it seems evident that for practical purposes a pocket such as Young and McCrea described should be considered a diverticulum.

Congenital defects and obstetrical trauma have frequently been given as causative factors in the production of urethral diverticula. Congenital diverticula are defects in the embryonic development of the urethra and are present at birth.

It appears more logical to assume that acquired urethral diverticula arise from retention cysts of the paraurethral ducts which, as the result of suppuration or trau-

8. Walker, L. M., and Huffman, J. W.: Adenocarcinoma of the Female Urethra: A Review, Quart. Bull., Northwestern Univ. M. School **21**:115, 1947.

9. Boyd, F. N.: Two Cases of Primary Carcinoma of the Female Urethra, J. Obst. & Gynaec. Brit. Emp. **9**:40, 1906.

10. Battle, W. H.: A Case of Carcinoma of the Urethra and Bladder, Lancet **2**:79, 1901.

11. McMurty, L. S.: Primary Carcinoma of the Female Urethra, Tr. Am. S. A. **26**:586, 1908.

12. Menville, J. G.: Primary Neoplasms of Female Urethra, Surg., Gynec. & Obst. **61**:229, 1935.

13. Clarke, C. M.: Observations on Those Diseases of Females Which Are Attended by Discharges, London, Longman [and others], 1814, p. 270.

14. Bozeman, N.: Urethrocele, Catarrh and Ulceration of the Bladder in Females, Am. J. Obst. **3**:636, 1871.

15. Young, B. R., and McCrea, L. E.: Urethrocele: Urethral Diverticulum; Suburethral Abscess in Female; Roentgen Appearance; Treatment; Review of Literature; Report of a Case, Urol. & Cutan. Rev. **41**:91, 1937.

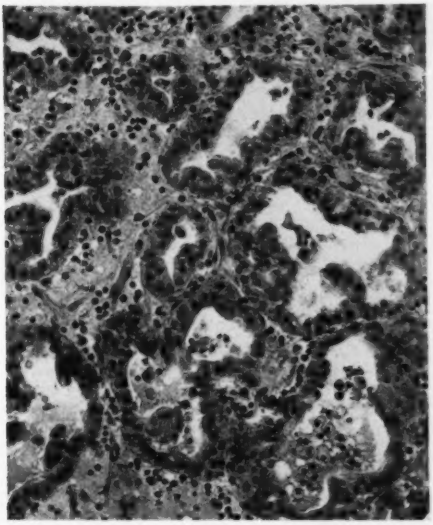


Fig. 10.—Adenocarcinoma of the female urethra of paraurethral duct origin. An exceedingly rare neoplasm histologically characterized by an acinar architecture and an epithelium resembling that of the paraurethral glands.

Fig. 11.—Urethrovaginal fistula near meatus. This lesion was a sequel to an acute infection in a paraurethral duct which ruptured into the vagina.

matism, rupture into the urethral lumen (fig. 6) rather than that they develop from tearing of the urethral musculature by obstetrical injury. Unquestionably, tearing of the fascial structures supporting the urethra by pressure of the fetal head on the dorsal urethral wall may be sufficient to rupture the urethrovaginal tissues, with the production of a urethral mucosal sacculation. It seems more likely, however, that traumatism of such a nature would produce a urethrocele rather than a pinhole-like hernial opening through which a typical small-necked pouch characteristic of urethral diverticula would form. Such a mechanism was described in one of the cases discussed by Priestley,[16] wherein a suburethral cyst was discovered during pregnancy. At the time of delivery the cyst ruptured into the urethra. Subsequently a urethral diverticulum developed at the site of the cyst.

Repeated obstruction, inflammation and rupture of a dilated paraurethral duct with poor drainage through the small duct lumen may so distend the sac that a urethra may establish a fistula (fig. 11). Trauma to or severance of a paraurethral ducts are the origin of many of the infected vaginal "cysts" and suburethral abscesses which produce urethral diverticula when the cyst or abscess ruptures into the urethral lumen.

Urethrovaginal Fistulas of Paraurethral Origin.—Urethrovaginal fistulas, other than those of traumatic origin, are rare lesions. A paraurethral duct abscess rupturing both into the urethra and into the vagina may create a urethrovaginal fistulous tract. In the same manner incision of a suburethral abscess connected with the urethra may establish a fistula (fig. 11). Trauma to or severance of a paraurethral duct at the time of an operation on the anterior vaginal wall undoubtedly is an explanation for some of the urethral fistulas which follow urethrocele repair and excision of urethral diverticula.

SUMMARY

The paraurethral ducts and glands comprise a mass of glandular and tubular structures about the female urethra. These homologs of the prostate gland are of clinical significance not only because they are foci for acute and chronic inflammations of the female urethra but also because of the diverse roles which they play in other lesions of the urethra and the urethrovaginal tissues. Suburethral abscesses develop in obstructed and infected retention cysts of the paraurethral ducts. These cysts and abscesses are important factors in the etiology of acquired urethral diverticula. Paraurethral duct cysts, while usually small, may reach considerable size, producing cystic tumefactions beneath the urethra and in the anterior vaginal wall. Benign (adenomas) and malignant (adenocarcinomas) tumors of the urethra may develop from paraurethral gland tissue. Urethrovaginal fistulas may follow rupture of paraurethral duct abscesses into the vagina and urethra or severance of the channel of a paraurethral duct during surgical procedures on the anterior vaginal wall.

CONCLUSIONS

The paraurethral ducts are of clinical significance in the following conditions: acute and chronic inflammation of the female urethra; periurethral and urethrovaginal cysts; anterior vaginal wall cysts; neoplasms of the urethra, including caruncles, adenomas and adenocarcinomas; abscesses of the urethrovaginal septum; suburethral abscesses; urethral acquired diverticula, and urethrovaginal fistulas.

16. Priestley, W. O.: Examples of Cyst Formation in the Neighborhood of the Female Urethra, Brit. M. J. **6**:1, 1869.

SUCCESSFUL RESECTION OF AN ANGIOENDOTHELIOMA OF THE CERVICAL ESOPHAGUS

Case Report and Review of the Literature

HAROLD K. PALANKER, M.D.
ANTHONY B. CONSTANTINE, M.D.
AND
JOHN R. PAINE, M.D.
BUFFALO

AMONG the recognized tumors of the esophagus, hemangioendotheliomas or lymphangioendotheliomas are extremely rare. We have been able to find only four cases reported. Three of these are to be found in the Italian literature, and one is in the American literature.

Frattin [1] in 1903 described a case of primary lymphangioendothelioma in the cervical portion of the esophagus originating in a diverticulum about 2 cm. below the cricoid cartilage. In 1910 Carrara [2] published a case of hemangioendothelioma of the esophagus that was discovered at autopsy. Macroscopically, this tumor resembled a carcinoma. Microscopically, however, many small neoplastic cells assuming both a cuboid and an oval shape were seen. The intimate grouping of these cells around vessels gave the impression that they were derived from the cells of the blood vessel walls, and hence the tumor was reported as a primary perivascular hemangioendothelioma of the esophagus.

In 1930 Mencarelli [3] reported an instance of periesophageal lymphangioma. At postmortem examination, a bizarre lesion was found in the lower third of the esophagus. The esophageal mucosa was intact, but a considerable amount of the esophagus was surrounded by a massive neoplasm. A cross section of the esophagus at this level showed a marked increase in the thickness of the tunica muscularis. The author described it as a "bulkiness of the entire region, surrounding the esophagus itself, more accentuated in the lower third." The tumor was firm, homogeneous and white. Several nodules of the same character, ranging in size from a pea to a hazelnut, were immediately adjacent to it. When examined histologically, the tumor was found to consist of a dense connective tissue stroma interspersed with scattered areas of infiltrating immature cells. In some sections there was a dense connective

From the Departments of Surgery and Pathology of the Buffalo General Hospital and the University of Buffalo School of Medicine.

1. Frattin, G.: Due casi di tumore primitivo in diverticoli del canale digerente, Policlinico (sez. chir.) **10**:502-512, 1903.

2. Carrara, N.: Sopra un caso di emangioendotelioma perivascolare primitivo dell'esofago, Gazz. internaz. med.-chir. **13**:117-121 (Nov.) 1910.

3. Mencarelli, L.: Linfangioendothelioma periesofageo, Riforma med. **46**:1705-1710 (Oct. 27) 1930.

tissue stroma surrounding multiple cystlike spaces. In contrast, the adjacent nodules showed multiple tubular formations, with the supporting stroma composed of relatively immature cells.

The only hemangioendothelioma of the esophagus reported in the American literature was discovered during life. This tumor was reported by Broders, Vinson and Davis [4] in 1933. The lower portion of the esophagus was involved. Esophagoscopy disclosed an infiltrating lesion of the left anterior wall which reduced the lumen considerably. Biopsy of material taken at the time of the esophagoscopy was reported as follows: "In a few areas of the specimen were groups of closely packed relatively small hyperchromatic round and oval neoplastic cells. For the most part, however, the specimen was made up of a network of small, ill defined blood vessels and spaces. These vessels and spaces were lined with endothelial cells that were indistinguishable from those that were closely packed. We believe that the presence of these neoplastic vessels represents an attempt of the tumor cells to differentiate and, therefore, is an indication of the lowering of the clinical malignancy. Occasionally mitotic figures appeared in both the solid and the vascular areas."

REPORT OF A CASE

Mrs. C. L., a 59 year old white woman, was admitted to the Buffalo General Hospital on Nov. 20, 1947, complaining of increasing difficulty in swallowing since September of 1947. There were times when she could swallow soft foods better than liquids. She had lost 6 pounds (2.7 Kg.) in weight since the onset of her symptoms. She gave no history of hoarseness or cough. In 1937 she was treated in a sanatorium for a tuberculous lesion of the upper lobe of the left lung. The patient was 2 years old when her mother died of tuberculosis. There was no history of cancer in the family.

The patient appeared well developed and well nourished. The pertinent physical findings consisted of a firm walnut-sized mass palpable on the right in the anterior cervical region just below and posterior to the cricoid cartilage. The mass was smooth, nontender and fixed to the posterior aspect of the larynx. The trachea appeared to be slightly deviated to the left. There was no evidence of any bruit or thrill. The regional lymph nodes did not appear to be enlarged.

Examination of the lungs revealed dulness and decreased breath sounds in the upper one third of the left side of the chest. Roentgen examination revealed the following: The esophagus was found to be sharply displaced to the right at the seventh cervical vertebra. At this point an irregularity, interpreted as a small ulceration, was present. The trachea at the same level was displaced anteriorly and to the left just above the clavicle. There was a diffuse homogeneous density throughout the apical portion of the left side of the chest.

Esophagoscopy on November 22 revealed a mass on the posterior wall of the esophagus at the level of the cricoid cartilage and apparently involving the left hypopharyngeal area. A biopsy at that time showed a moderate hyperplasia of the esophageal mucosa associated with a localized inflammatory infiltration consisting mostly of lymphoid cells, disintegrating leukocytes and some fibroblasts. A second esophagoscopy performed on December 1 showed a definite constriction of the esophagus at the hypopharynx, caused by an apparent thickening of the posterior esophageal wall. There was also an area of granulation tissue on the posterior edge of the cricoid cartilage. The impression of the esophagoscopist was that this lesion was probably an infiltrating carcinoma. Several biopsies showed only diffuse inflammatory changes, with considerable edema.

In spite of the fact that the biopsies of material obtained at esophagoscopy were all reported as failing to show the presence of a neoplasm, it was decided to operate on the patient. One of us (J. R. P.) was convinced from the symptoms and the clinical picture that she probably had a malignant lesion. A gastrostomy for future feeding was made first. Then a week later, on

4. Broders, A. C.; Vinson, P. P., and Davis, P. L.: Hemangioendothelioma of the Esophagus: Report of a Case, Arch. Otolaryng. **18**:168-171 (Aug.) 1933.

December 5, the definitive operation was performed. In general, Wookey's [5] technic of cervical esophagectomy was followed. A large rectangular skin flap including the platysma muscle was raised from the anterior aspect of the patient's neck and retracted to the right. When the deeper structures of the neck were exposed, a hard rubbery lesion was found which involved the upper 2 inches (5 cm.) of the cervical portion of the esophagus and invaded the posterior aspect of the larynx. This lesion had the clinical characteristics of a neoplasm, but it was necessary to excise three portions for immediate examination by frozen section before the pathologist could definitely confirm its neoplastic and malignant character. This point finally having been determined, a radical resection of the cervical esophagus, the larynx, the upper portion of the trachea and the right lobe of the thyroid gland was carried out. A permanent tracheotomy was constructed just above the manubrium, and the continuity of the esophagus was partially reestablished by infolding and suturing the skin flap to the mucous membrane

Fig. 1.—Roentgenogram of the esophagus prior to surgical intervention. Note the deformity of the esophagus at the level of the sixth and seventh cervical vertebrae. The trachea as well as the esophagus is slightly deviated to the left and displaced anteriorly. The opinion of the radiology department was that of an intrinsic lesion of the esophagus, most probably a malignant growth.

of the hypopharynx above and to the distal cut end of the esophagus behind the manubrium below. A deep skin-lined trough was thus constructed. No enlarged lymph nodes were felt or seen during the operation, and no lymph node dissection was performed, for the operator assumed that he was dealing with some sort of sarcoma. A split thickness skin graft was employed to cover the residual skin defect on the left anterior surface of the neck.

Six weeks were allowed to elapse before the reconstruction of the esophagus was completed by converting the skin trough into a skin tube. During this interval, the patient was able to

5. Wookey, H.: Surgical Treatment of Carcinoma of the Pharynx and Upper Esophagus, Surg., Gynec. & Obst. **75**:499-506 (Oct.) 1942.

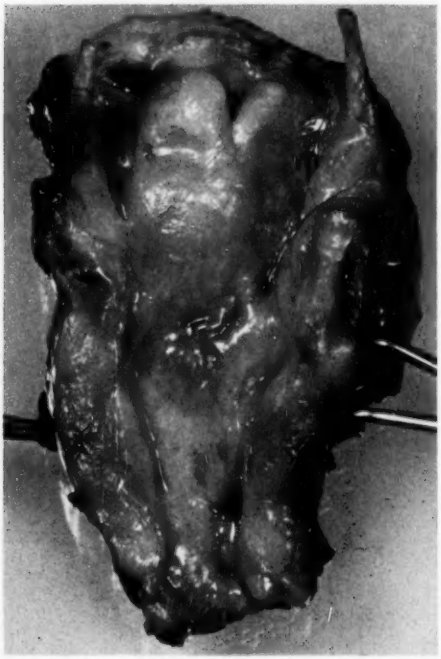


Fig. 2.—The gross appearance of the resected specimen, consisting of esophagus and larynx. Note the thickened wall of the esophagus caused by tumor infiltration. Note also the intact esophageal mucosa.

Fig. 3.—Appearance of patient about 40 days after total laryngectomy, partial esophagectomy and partial thyroidectomy, tracheotomy and skin graft.

swallow and convey through the trough the major part of the required fluids and nourishment. Roentgen examination carried out on Jan. 27, 1948, showed that the reconstructed esophagus was of good caliber. Fluids and soft foods could be taken without difficulty. Convalescence was complicated by the formation and persistence of a small fistula at the lower angle of the wound. Five attempts were made to close this fistula surgically, but all were unsuccessful. The patient was finally discharged from the hospital on April 3, 1948, with the fistula still open. It closed spontaneously, however, one week after she returned home. Normal weight and good health returned rapidly. The patient has remained well, with no evidence of recurrence or metastasis up to the time she was last seen, on Nov. 1, 1950. She can eat and swallow all types of food, only occasionally having to wash these down with fluid.

Pathologic Report.—The gross specimen consisted of the entire larynx, the upper portion of the trachea, including three cartilaginous rings, the upper portion of the esophagus, a portion

Fig. 4.—Roentgenogram of the reconstructed esophagus seven weeks after operation. Note the satisfactory caliber and the free passage of the barium into the esophagus below.

of the hypopharynx with the epiglottis and the right lobe of the thyroid. The hypopharynx and the portion of the esophagus measured 9 cm. in length. Beginning with the esophagopharyngeal junction, the esophageal wall was involved by a constricting new growth, which completely infiltrated the wall. The new growth extended downward about 4.2 cm. along the esophageal tube. The esophageal wall in this area averaged 1 cm. in thickness. The lesion produced a distinct degree of stenosis, barely admitting a lead pencil at its narrowest point. The mucosa overlying this area showed no ulcerations, but there were several low nodular protrusions. The thickened anterior wall of the esophagus was intimately fused with the contiguous membranous portion of the trachea. The posterior aspect of the right lobe of the thyroid was also firmly adherent to the esophageal wall. A cuff of normal esophageal wall about 1 cm. in length was present at the distal end of the specimen. The hypopharyngeal mucosa was smooth, but there was evidence of edema of the aryepiglottic folds. The grayish white cut surface of the tumor

was distinctly fibrous, almost cartilaginous in appearance. The lobe of thyroid attached was not remarkable grossly except for its firm fibrous attachment to the tumor posteriorly.

Various sections through the tumor showed proliferating tumor cells, for the most part growing diffusely, but often forming small cystlike spaces. Most of these spaces appeared empty, but many were seen to contain pinkish protein-rich coagulum. Rarely red blood cells were seen within the spaces. The cells were small and rounded and only occasionally assumed a polyhedral shape. When lining the spaces, they appeared flattened and endothelial in nature. In some areas they were compressed by connective tissue stroma and assumed an elongated or spindle outline. The round to oval-shaped nuclei were vesicular in type, with a well defined nuclear membrane containing several minute nucleoli. Mitotic figures were seen occasionally. The cells

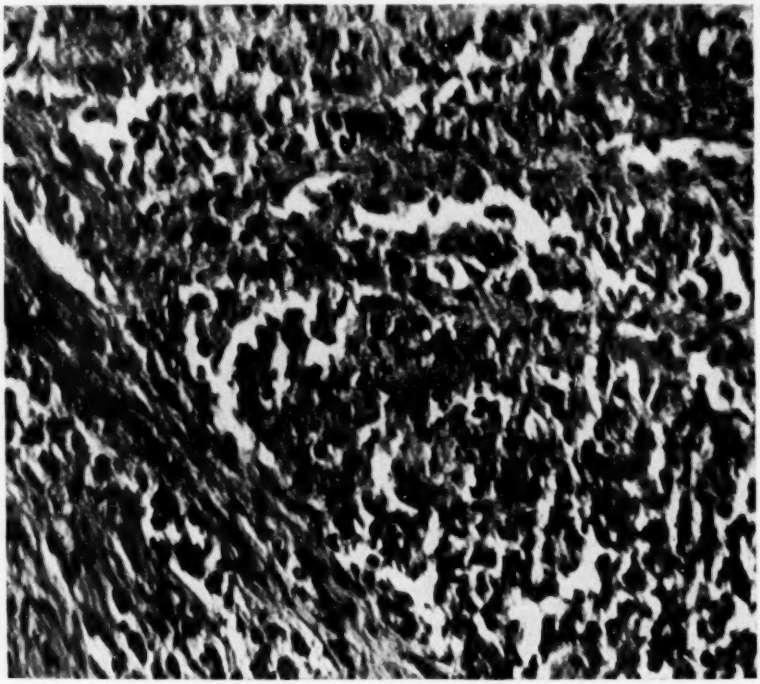


Fig. 5.—The microscopic appearance of the tumor showing proliferating tumor cells, for the most part growing diffusely but often forming spaces lined by tumor cells. The muscle coat is involved predominantly.

contained no fibrils; no striations could be demonstrated with Mallory's phosphotungstic acid hematoxylin stain, and no giant cells were present. These cells had all the characteristics associated with the endothelial type of cell. Throughout the tumor, varying amounts of desmoplastic reaction was seen associated with the endothelial proliferation. In some areas the bulk of the tumor was made up of fibrous tissue, with a few of the endothelial cells compressed between the fibers, whereas in other places the endothelial elements predominated, forming small sinusoidal spaces supported by minimal fibrous stroma. The bulk of the tumor occupied and infiltrated the muscle coat, only occasionally involving the mucosa. The majority of the muscle fibers were destroyed, but here and there isolated bundles and individual muscle fibers of both smooth and striated types were seen surrounded and compressed by infiltrating tumor.

The overlying epithelium was generally intact, but in the areas where the tunica propria was involved the stratified squamous epithelium appeared thin and eroded, with minimal chronic inflammatory changes superficially. At the periphery the tumor blended into a zone of fibrosis. The growth infiltrated to the perichondrium of the cricoid cartilage and the capsule of the thyroid. No blood pigments were seen anywhere in the tumor.

COMMENT

This tumor demonstrates most of the criteria discussed by Ewing [6] as characteristic of endotheliomas. Typically, the neoplastic endothelial cells are small, with an oval, vesicular nucleus and minute multiple nucleoli. Their outline varies, depending on their relation to the stroma. When growing in diffuse sheets they tend to be polyhedral; when lining the spaces they tend to assume a flattened simple squamous-like contour, while in areas with abundant fibrous stroma they assume a blunt spindle shape which closely resembles that of fibroblasts. Many pathologists feel that the intimate relationship of the cells to the supporting stroma is a most important criterion. The desmoplastic properties of many endotheliomas also assist in their recognition.

Two classifications of endotheliomas have been offered. That of Borrman [7] is based on the histiogenesis of the tumor, while that of Ewing [6] is based on the morphology of the tumor. According to Ewing's classification, the tumor reported in this communication would be classified as an angioendothelioma, since it characteristically formed small sinusoidal spaces lined with endothelium-like cells. If Borrman's classification be followed, this tumor should probably be called a lymphangioendothelioma inasmuch as no blood cells were seen in the sinusoids and there was a complete absence of any blood pigments throughout the tumor.

The results of the excision of malignant tumors of the cervical portion of the esophagus have been, in general, discouraging. Only two or three instances of survival beyond five years are reported. The great majority of such lesions are carcinomas, and most patients treated by excision have died within two years following operation with cervical lymph node metastases. In the present instance it is our hope that the prognosis is good. No lymph node involvement was noted at the time of operation and no evidence of metastases has occurred during the three year interval since operation.

SUMMARY

A rare tumor of the cervical portion of the esophagus in a 59 year old white woman has been described. According to Borrman's classification of endotheliomas, it should be considered to be a lymphangioendothelioma. According to Ewing's classification, it should be considered to be an angioendothelioma.

The patient was treated by radical resection of the cervical portion of the esophagus and the larynx. She is alive and well, with no signs of recurrence or metastases two years and 11 months later.

---

6. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 335-385.

7. Borrman, in Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 335-385.

PHEOCHROMOCYTOMA

Anesthetic Management During Surgical Treatment

VIRGINIA APGAR, M.D.
AND
E. M. PAPPER, M.D.
NEW YORK

PATIENTS with pheochromocytoma pose several challenges of theoretical and practical importance. The problem of the relationship between hyperfunction of chromaffin tissue and hypertension is brought forward in this lesion. Secondly, only hypertension which is caused by a pheochromocytoma can be cured completely by surgical treatment. Finally, the presence of large quantities of circulating epinephrine and arterenol (nor-epinephrine) in the blood of these patients poses serious and difficult problems in anesthetic management. These have a significant bearing on the current high operative mortality rate (approximately 20 per cent).

Since pheochromocytoma is an uncommon lesion which has so many facets of interest, a review of the literature was undertaken together with a summary of the experience gained in the operative management of this disease at the Presbyterian Hospital. Criteria for inclusion in this survey were signs and symptoms of hyperadrenalemia and a proved pheochromocytoma at operation or autopsy. Patients without these criteria were excluded from consideration.

PREVIOUS OBSERVATIONS

The clinical entity of pheochromocytoma is comparatively new. The tumor of adrenal medullary cells was discovered in the pathological laboratory in 1886.[1] It was first found at operation in 1923,[2] although the attempt at removal was unsuccessful. In 1927 [3] Mayo first excised such a tumor successfully but without making the diagnosis preoperatively. The first correctly diagnosed and successfully removed tumor was reported in 1929.[4]

Read before the Section on Anesthesiology at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 28, 1950.

From the Department of Surgery (Anesthesiology), College of Physicians, Columbia University, and the Anesthesia Service of Presbyterian Hospital.

1. Fränkel, F.: Ein Fall von doppelseitingem, völlig latent verlaufenen Nebennierentumor und gleichzeitiger Nephritis mit Veränderungen am Circulationsapparat und Retinitis, Arch. f. path. Anat. **103**:244-263, 1886.

2. Masson, P., and Martin, J. F.: Paranganglíome surrénal, étude d'un cas humain de tumeurs malignes de la médullo-surrénale, Bull. de l'Assoc. franc. p. l'étude de cancer **12**:135-143, 1923.

3. Mayo, C. H.: Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve: Report of Case, J. A. M. A. **89**:1047-1050 (Sept. 24) 1927.

4. (*a*) Pincoffs, M. C.: Case of Paroxysmal Hypertension Associated with Suprarenal Tumor, Tr. A. Am. Physicians **44**:295-299, 1929. (*b*) Shipley, A. M.: Paroxysmal Hypertension Associated with Tumor of Suprarenal, Ann. Surg. **90**:742-749 (Oct.) 1929.

Pheochromocytomas are unique in that the serious and fatal consequences of the disease are associated with an excessive secretion of epinephrine and arterenol. Histologically, they are usually benign; physiologically they are malignant. If the tumor is not removed, death from cerebrovascular accident or cardiac failure with pulmonary edema as the end result of paroxysmal hypertensive disease can be expected within about 10 years from the onset of symptoms. Smithwick estimates that about 0.5 per cent of cases with hypertension are caused by this disease.[5] Although this group is comparatively small, its importance is great since complete cure is possible in contrast to the palliation effected in the therapy of other types of hypertension. The disease occurs equally in both sexes. The age incidence is widespread, varying from 1½ months to 68 years. In over 90 per cent of the reported cases the tumor was histologically benign. Local or widespread metastases to bone or brain were observed in the others. The location of the tumor is usually in one of the adrenal glands, less often in the lumbar area in the region of the sympathetic chain and in the organ of Zuckerkandl at the bifurcation of the aorta, while at least four have been found in the chest or brain. The tumor is single in about 85 per cent of the cases and multiple in 15 per cent.

The clinical picture of pheochromocytoma has been summarized recently by Smithwick and others.[6] Outstanding is the hypertension, usually paroxysmal in nature but occasionally consistently high, especially in children. Sweating is universal and frequently severe. Evidence of peripheral vasoconstriction during attacks is an almost constant finding. Other less frequently described symptoms are headache, vomiting and a sense of impending death during the acute episodes.

Among the usual objective findings are those associated with an elevated body temperature and basal metabolic rate. Postural tachycardia and hypotension were noted in half of Smithwick's cases. An increased fasting blood sugar level and a diabetic glucose tolerance curve are common. An abdominal mass, massage of which will reproduce an attack of paroxysmal hypertension, is infrequent but highly suggestive when present.

DIAGNOSTIC TESTS

Since 1932 numerous diagnostic tests have been suggested as more or less specific. Of the many proposed there are only three which appear to have the advantage of simplicity and accuracy as a diagnostic weapon. The three which are described below should be used in any given patient suspected of suffering from this disease.

A. Benzodioxan test.[5] Intravenous administration of 10 mg. of benzodioxan (diluted to 2 cc.) per square meter of body surface in a period of one minute will reduce the blood pressure sharply in a patient with pheochromocytoma because of the adrenolytic action of the drug. Benzodioxan produces either no change or a slight elevation of arterial pressure in patients with essential hypertension or in normotensive persons. Since this test was described, 59 of 62 patients with proved pheochromocytoma gave a positive reaction.[7] There were only three false negative reactions in this group. The test is not specific for epinephrine-secreting tumors

5. Goldenberg, M.; Snyder, C. H., and Aranow, H., Jr.: New Test for Hypertension Due to Circulating Epinephrine, J. A. M. A. **135**:971-976 (Dec. 13) 1947.

6. Smithwick, R. H.; Greer, W. E. R.; Robertson, C. W., and Wilkins, R. W.: Pheochromocytoma, New England J. Med. **242**:252-258 (Feb. 16) 1950.

7. Goldenberg, M.: Personal communication to the authors.

alone but also will depress hypertension due to arterenol. Since pheochromocytomas contain both substances, the test is almost specific. Calkins [8] recently reported a positive reaction to the benzodioxan test in a child with a proved malignant neuroblastoma.

B. Cold pressor test. In almost all hypertensive patients, immersion of the forearm in ice water for one minute will cause a rise of over 20 mm. Hg systolic and 15 mm. Hg diastolic pressure. Patients in whom pheochromocytomas are responsible for the hypertension do not have a positive reaction to the cold pressor test.

C. Histamine test.[9] When 0.05 mg. of histamine is injected intravenously, a typical paroxysmal hypertensive crisis is produced in patients with pheochromocytoma. Patients with hypertension from other causes will show some rise in blood pressure but much less in degree when compared with those having pheochromocytoma. Because of the severity of symptoms, it is well to have some sympathetic blocking agent such as benzodioxan at hand to reverse the acute hypertensive episode.

Many other tests involving the use of sympathetic stimulants and blocking agents have been described, but all have certain objections, such as nonspecificity or side actions, which make their use unwise. Epinephrine, methacholine chloride (mecholyl® chloride), tetraethylammonium salts and dibenamine® (N, N-dibenzyl-beta-chloroethylamine) have all been used for diagnostic purposes.

Demonstration of a tumor in the adrenal region by intravenous or retrograde pyelography or by air injections into the perirenal area has been moderately successful, according to Cahill.[10] Obviously tumors located in areas other than the adrenal area will not be demonstrated by this method. Likewise a mass demonstrated in the adrenal area may be cortical rather than medullary in origin, but the clinical pictures of cortical and medullary tumors of the adrenal gland are sufficiently different so that differential diagnosis is not difficult. In fact, among the reported cases of pheochromocytoma there are only two in which symptoms of cortical dysfunction were present in addition to the usual symptoms of medullary hyperactivity.[11]

No specific electrolyte changes in the blood have been described. Our two patients who died had high concentrations of potassium in the blood and in the spinal fluid immediately after their death, but these could have been postmortem changes. There are instances in which potassium levels were reported to be normal in this disease.[12]

8. Calkins, E., and Howard, J. E.: Bilateral Familial Phaeochromocytomata with Paroxysmal Hypertension: Successful Surgical Removal of Tumors in 2 Cases, with Discussion of Certain Diagnostic Procedures and Physiological Considerations, J. Clin. Endocrinol. **7**:475-492 (July) 1947.

9. Roth, G. M., and Kvale, W. F.: Tentative Test for Pheochromocytoma, Am. J. M. Sc. **210**:653-660 (Nov.) 1945.

10. Cahill, G. F.: Hormonal Tumors of Adrenal, Surgery **16**:233-265 (Aug.) 1944.

11. Neff, F. C.; Tice, G. M.; Walker, G. A., and Ockerblad, N.: Adrenal Tumor in Female Infant with Hypertrichosis, Hypertension, Overdevelopment of External Genitalia, Obesity, but Absence of Breast Enlargement, J. Clin. Endocrinol. **2**:125-127 (Feb.) 1942. Cahill.[10]

12. (*a*) Goldner, M. G.: Pheochromocytoma with Diabetes: Case Report and Discussion, J. Clin. Endocrinol. **7**:716-723 (Oct.) 1947. (*b*) Snyder, C. H., and Vick, E. H.: Hypertension in Children Caused by Pheochromocytoma: Report of 3 Cases and Review of Literature, Am. J. Dis. Child. **73**:581-601 (May) 1947.

ANESTHESIA USED DURING OPERATION

Examination of all reported cases in the literature in which operation was performed was completed to summarize the currently available information concerned with anesthetic management. Some difficulty was presented by multiple reports of the same case. One patient, M. M., has been the subject of five different papers,[13] while another, J. L., has been reported on four times.[14]

Of the 91 patients reported to date, 15 were subjected to other operative procedures before the correct diagnosis was made.[15] In addition there are records of 16 other patients in whom pheochromocytoma was found at autopsy and in whom an unrelated operation had recently been performed.[16] Fifteen of these 16 patients died from two to 48 hours postoperatively in irreversible shock. One patient died

13. Engel, F. L.; Mencher, W. H., and Engel, G. L.: "Epinephrine Shock" as Manifestation of Pheochromocytoma of Adrenal Medulla: Report of Case with Successful Removal of Tumor, Am. J. M. Sc. **204**:649-661 (Nov.) 1942. Mencher, W. H.: Paroxysmal Hypertension Caused by Pheochromocytoma of the Adrenal Gland, J. Mt. Sinai Hosp. **10**:743-746 (Jan.-Feb.) 1944. Hyman, A., and Mencher, W. H.: Pheochromocytoma of Adrenal Gland, J. Urol. **49**:755-776 (June) 1943. Colston, J. A. C.: Surgical Aspects of Bilateral Familial Pheochromocytoma, Tr. Am. A. Genito-Urin. Surgeons **39**:81-105, 1947. Calkins and Howard.[8]

14. Cahill, G. F.: Pheochromocytomas, J. A. M. A. **138**:180-186 (Sept. 18) 1948. Ganem, E. J., and Cahill, G. F.: Pheochromocytomas Coexisting in Adrenal Gland and Retroperitoneal Space, with Sustained Hypertension: Report of Case with Surgical Care, New England J. Med. **238**:692-697 (May 13) 1948. Goldenberg and others.[5] Snyder and Vick.[12b]

15. (*a*) Brunschwig, A., and Humphreys, E.: Excision of Pheochromocytoma Following Near Fatal Attack of Paroxysmal Hypertension, J. A. M. A. **115**:355-357 (Aug. 3) 1940. (*b*) Bartels, E. C., and Arnold, W. T.: Essential Features for Diagnosis of Pheochromocytoma: Report of a Case, Lahey Clin. Bull. **6**:132-142 (July) 1949. (*c*) La Due, J. S.; Murison, P. J., and Pack, G. T.: Use of Tetraethylammonium Bromide as Diagnostic Test for Pheochromocytoma, Ann. Int. Med. **29**:914-921 (Nov.) 1948. (*d*) Hatch, F. N.; Richards, V., and Spiegl, R. J.: Adrenal Medullary Tumor (Pheochromocytoma), Am. J. Med. **6**:633-642 (May) 1949. (*e*) Hamilton, J. E.: Pheochromocytoma of Adrenal with Paroxysmal Hypertension, Case Relieved by Surgery, Kentucky M. J. **38**:572-575 (Dec.) 1940. (*f*) Kvale, W. F.; Roth, G. M.; Clagett, O. T., and Dockerty, M. B.: Headache and Paroxysmal Hypertension: Observations Before and After Surgical Removal of Pheochromocytoma, S. Clin. North America **24**:922-933 (Aug.) 1944. (*g*) MacKeith, R.; Adrenal-Sympathetic Syndrome; Chromaffin Tissue Tumour with Paroxysmal Hypertension, Brit. Heart J. **6**:1-12 (Jan.) 1944. (*h*) Spear, H. C., and Griswold, D.: Use of Dibenamine in Pheochromocytoma: Report of a Case, New England J. Med. **239**:736-739 (Nov.) 1948. (*i*) Pincoffs.[4a] Calkins and Howard.[8] (*k*) Cahill.[10]

16. von Neusser, E.: Die Erkrankungen der Nebennieren, ed. 2, Vienna, Alfred Hölder, 1910, p. 97. Helly, K.: Zur Pathologie der Nebenniere, München. med. Wchnschr. **60**:1811, 1913. Herde, M.: Zur Lehre der Paranganglione der Nebenniere, Arch. f. klin. Chir. **97**:937-951, 1912. Hedinger, E.: Struma medullaris cystica suprarenalis (Beitrag zur Lehre der Paraganglione), Frankfurt. Ztschr. f. Path. **7**:112-126, 1911. Bartels, E. C., and Wall, N. M.: Clinical Problem of Pheochromocytoma, S. Clin. North America **27**:605-615 (June) 1947. McCullagh, E. P., and Engel, W. J.: Pheochromocytoma with Hypermetabolism: Report of 2 Cases, Ann. Surg. **116**:61-75 (July) 1942. Wells, A. H., and Boman, P. G.: Clinical and Pathologic Identity of Pheochromocytoma: Report of Case, J. A. M. A. **109**:1176-1180 (Oct. 9) 1937. Oberling, C., and Jung, G.: Paranganglione de la surrénale avec hypertension paroxystique, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:366-371 (March 24) 1927. Handschin, E.: Zur Kenntnis der Zuckerkandl'schen Organe, Beitr. z. path. Anat. u. z. allg. Path. **79**:728-755 (April 16) 1928. King, E. S. J.: Malignant Phaeochromocytoma of Adrenals, J. Path. & Bact. **34**:447-452 (July) 1931. Paul, F.: Die krankhafte Funktion der Nebenniere und ihr gestaltlicher Ausdruck, Virchows Arch. f. path. Anat. **282**:256; 327, 1931. Cahill.[10]

several months after an uneventful thyroidectomy.[17] The mortality rate in the group of patients suspected of having pheochromocytomas was 24 per cent, while in the unsuspected group it was slightly over 50 per cent. This difference in mortality demonstrates clearly the need to avoid unrelated surgical manipulations in patients with pheochromocytoma. Only the most urgent surgical procedures for emergency conditions should be undertaken, and then with the immediate availability of sympatholytic and vasopressor drugs. If an elective situation exists, it is wiser to remove the pheochromocytoma first after the diagnosis has been established. The development of a high index of suspicion in patients with labile hypertension will be of great help in minimizing the dangers of ill advised operation in patients with pheochromocytoma.

In over half of the cases in which operation was performed for pheochromocytoma, the type of anesthetic agent or technic was not mentioned. In 41 cases there is some reference to the anesthetic agent. In 22 patients ether was the principal anesthetic agent, and in five patients cyclopropane was utilized, usually in combination with ether. Spinal anesthesia was administered seven times. Ethylene was reported used three times, vinyl ether (vinethene) twice, tribromethanol "several times" and thiopental sodium (pentothal®) twice. The relationship between mortality and morbidity and anesthetic agent or technic cannot be defined clearly from the data available. There appears to be no agreement in the literature on the most desirable means of anesthetic management. A sequence of tribromethanol, ether and oxygen was recommended by Espersen and others,[18] and by Cahill and Aranow.[19] Spinal anesthesia was mentioned favorably by Bauer and Belt [20] because of the great degree of surgical relaxation needed. LaDue and others [15c] recommended unilateral spinal anesthesia with a light dibucaine hydrochloride (nupercaine®) solution to preserve the afferent fibers of the opposite splanchnic nerves, a rather unlikely probability. Espersen and others [18] mention the difficulty of controlling blood pressure levels during spinal anesthesia.

In the group of unsuspected pheochromocytomas, proved at some subsequent time, the type of operation unrelated to the correction of this disease was as variable as the choice of anesthesia. The usual postoperative history was one of severe and irreversible circulatory collapse, with death in from two hours to two days.

PRESENT OBSERVATIONS

Our own experience with pheochromocytoma includes 12 operations on 10 patients for the removal of the tumor. Eight of these survived. Four other patients with unsuspected pheochromocytoma were operated on for other lesions. All died, and the tumor was found at autopsy. In addition, exploration has been performed in 14 patients without demonstrating the tumor at operation. Our cases are included

17. B. N., reported in table 2.

18. Espersen, T., and Dahl-Iversen, E.: Clinical Picture and Treatment of Pheochromocytomas of Suprarenal: Two Own Cases, One with Paroxysmal Hypertension Improved by Treatment with Methylthiouracil and Cured by Surgical Intervention, Acta chir. Scandinav. **94**:271-290, 1946.

19. Cahill, G. F., and Aranow, H., Jr.: Pheochromocytoma: Diagnosis and Treatment, Ann. Int. Med. **31**:389-404 (Sept.) 1949.

20. Bauer, J., and Belt, E.: Paroxysmal Hypertension with Concomitant Swelling of Thyroid Due to Pheochromocytoma of Right Adrenal Gland: Cure by Surgical Removal of Pheochromocytoma, J. Clin. Endocrinol. **7**:30-46 (Jan.) 1947.

in the previous total figures, while two of the pheochromocytoma cases and four of the unsuspected cases have not been previously reported. In six other cases

TABLE 1.—*Data on Patients Operated on for Pheochromocytoma**

Patient	Sex	Age	Premedication	Anesthesia	Complications During Operation	Post-operative Therapy	Period of Follow-Up
D. P.[10]	F	26	Morphine sulfate, 15 mg.; atropine, 0.6 mg.	Cyclopropane ether endotracheal	Cardiac arrest, irreversible	....	....
D. B.[12b]	F	11	Secobarbital, 45 mg.; scopolamine, 0.4 mg.; tribromethanol, 77 mg./Kg.	Nitrous oxide ether; endotracheal	Cardiac arrest, irreversible	....	....
E. R.[10]	F	29	Pentobarbital, 100 mg.; morphine sulfate, 12 mg.; scopolamine, 0.5 mg.;	Nitrous oxide ether	Moderate drop of blood pressure	High voltage roentgen ray therapy	9 yr.
K. G.[14]	F	42	Morphine sulfate, 9 mg.; scopolamine, 0.4 mg.; tribromethanol, 50 mg./Kg.	Cyclopropane endotracheal	5 doses neosynephrine	Desoxycorticosterone, 5 mg.; epinephrine in oil, 3 times	3 yr.
E. C.†	F	49	Morphine sulfate, 12 mg.; atropine, 0.4 mg.; tribromethanol, 90 mg./Kg.	Nitrous oxide ether	Rib broken	None	10 yr.
J. S.[10]	F	48	Morphine sulfate, 12 mg.; atropine, 0.4 mg.	Nitrous oxide ether	None	None	8 yr.
M. E.	F	49	Morphine sulfate, 12 mg.; atropine, 0.3 mg.	Thiopental sodium nitrous oxide ether	Arterenol drip for hypotension	Infusion continued 24 hr.	8 mo.
H. B.	M	42	Morphine sulfate, 12 mg.; atropine, 0.4 mg.	Thiopental sodium nitrous oxide ether; endotracheal	Pneumothorax arterenol infusion	Infusion continued 48 hr.	8 mo.
J. L.[12b]	F	11	Secobarbital, 90 mg.; scopolamine, 0.4 mg.	Ether	Epinepherine intravenously and in oil	Cortisone; symptoms persisted	....
			Secobarbital, 60 mg. morphine sulfate, 10 mg.; scopolamine, 0.4 mg.	Nitrous oxide ether	None	None	6 yr.
P. D.[14]	M	11	Codeine, 30 mg.; scopolamine, 0.3 mg.	Thiopental sodium nitrous oxide	None; tumor infarcted	None; 3 years later mediastinal shadow re-explored	....
		14	Meperidine hydrochloride, 75 mg.; scopolamine, 0.4 mg.	Thiopental sodium cyclopropane ether; endotracheal	None	None	4 yr.

* Twelve operations were carried out on 10 patients, with eight survivals. Two deaths occurred during operation; there were no postoperative deaths.
† Reported by Heath, P. K.; Cahill, G. F., and Atchley, D. W.: J. A. M. A. 117:1258 (Oct. 11) 1941.

TABLE 2.—*Data on Patients with Unsuspected Pheochromocytoma**

Patient	Sex	Age	Operation	Premedication	Anesthesia	Complications	Time of Death
P. S.	F	53	Laparotomy; hemorrhagic mass above left kidney	Morphine sulfate, 9 mg.	Ether	Excessive mucus	2 hr.
B. N.	F	49	Thyroidectomy	Morphine sulfate, 12 mg.; atropine, 0.4 mg.	Cyclopropane, tribromethanol	No improvement in symptoms; cardiac failure	4 yr.
T. P.	M	44	Biopsy of retroperitoneal mass	Morphine sulfate, 12 mg.; scopolamine, 0.4 mg.	Cyclopropane, nitrous oxide; endotracheal	Pulmonary edema	17 hr.
M. H.	F	53	Biopsy of carcinoma of breast	Meperidine hydrochloride, 100 mg.; scopolamine, 0.4 mg.	Thiopental sodium, nitrous oxide	Cyanosis, restless	3 hr.

* Presence of tumor proved at autopsy.

in our clinic pheochromocytoma has been found at autopsy, but since no symptoms of hyperadrenalemia were present, they have been omitted from this series.

The pheochromocytoma cases are summarized in table 1 and the unsuspected cases in table 2.

The two fatal cases in this series have been reported elsewhere but are summarized here from the standpoint of anesthetic management.

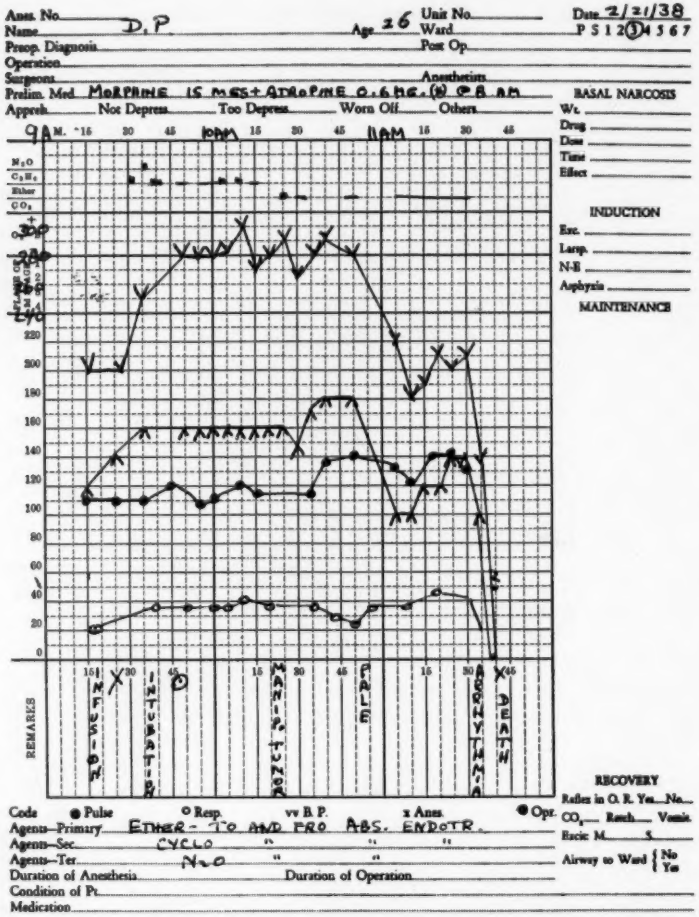


Fig. 1.—Chart of patient with symptoms of hyperadrenalemia for eight years. Exploration seven years before revealed no adrenal tumor. Retinal changes were marked, and there were paroxysms of hypertension. A large malignant tumor of the left adrenal gland was found invading the aorta and vena cava. During manipulation of the tumor, the blood pressure dropped sharply and the patient died. Direct cardiac massage revealed a markedly contracted heart.

REPORT OF CASES

CASE 1 (fig. 1).—D. P.[10] was a 26 year old white woman complaining of attacks of sweating, coldness of the extremities, palpitation and proved hypertension since 1930 (eight years before her admission to the hospital). Her vision had grown progressively worse during that time. Laparotomy in 1931 did not disclose a pheochromocytoma.

Prior to a second exploratory laparotomy in February of 1938, the blood pressure was 280/160. Her basal metabolic rates were + 35 and + 55 on two occasions. The glucose tolerance test suggested diabetes. After preparation with eschatin,[9] she was given morphine, 15 mg., and atropine, 0.6 mg. Anesthesia was begun 85 minutes later with cyclopropane, and an oral endotracheal airway was inserted. Ether was added later to improve muscular relaxation.

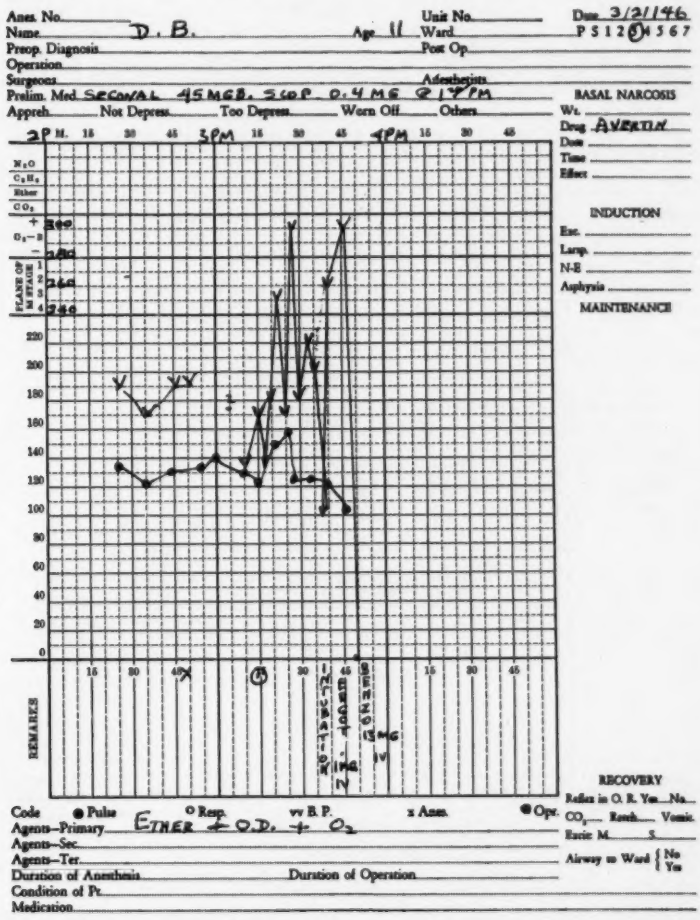


Fig. 2.—Chart of patient with hyperhidrosis. There was a positive benzodioxan reaction, and aerograms and pyelograms were normal. Retinal changes were present. Two extra-adrenal tumors were found. The patient died during exploration.

A large tumor invading the inferior vena cava and the aortic wall was found in the region of the left adrenal gland. After a period of difficult dissection and manipulation, the patient appeared pale and suffered an acute episode of hypotension. After a brief rallying period, complete circulatory collapse occurred. Cardiac massage through a diaphragm incision was unsuccessful as a resuscitative measure. Cessation of cardiac action had occurred in marked systolic

contraction. The serum potassium at the time of death was 35 mg. per 100 cc., compared to a preoperative level of 16 mg. per 100 cc. The former value was probably incorrect because of hemolysis. However, the spinal fluid was also examined and contained 40 mg. per 100 cc., approximately three times the normal value. The tumor was histologically malignant.

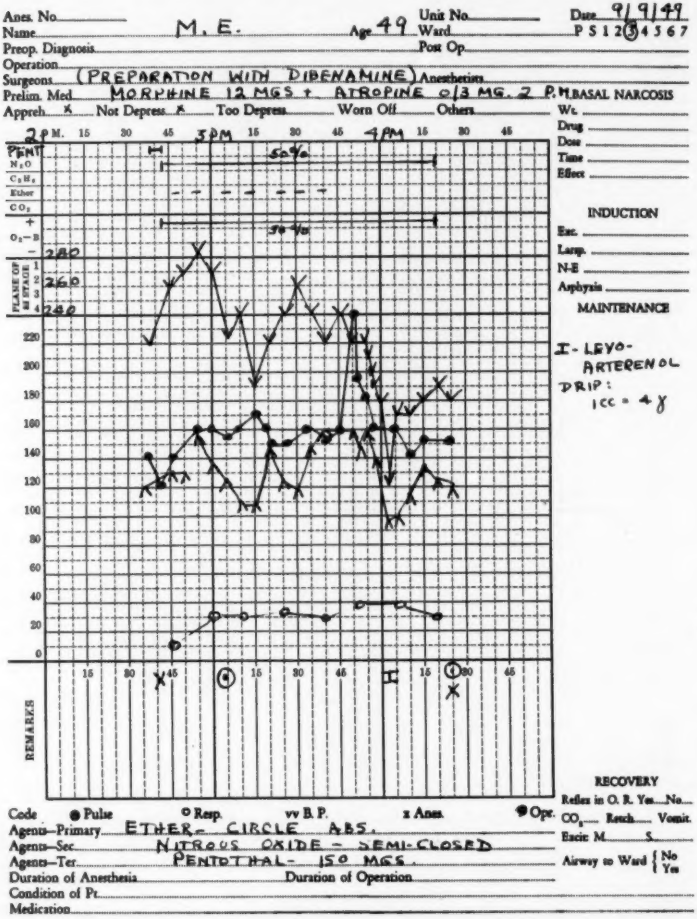


Fig. 3.—The patient had symptoms for one year. Weight decreased to 68 pounds (30.8 Kg.). Dibenamine® was administered twice, both times accompanied with right hemiparesis. Hypertension during operation was not prevented by the use of dibenamine.® Arterenol infusion was used to control hypotension during and after operation. Good recovery with gain in weight of 34 pounds (15.4 Kg.) occurred in six months.

Case 2 (fig. 2).—D. B.[12b] was an 11 year old child with a history of profuse sweating and nervousness which became continuous in nature after a preliminary period of remissions. The preoperative blood pressure was 210/160. The benzodioxan test gave a positive reaction. Adrenal aerograms were of little value. In March 1946 the patient was prepared for operation

with secobarbital sodium (seconal® sodium) 45 mg., and scopolamine, 0.4 mg., followed by 80 mg. per kilogram of tribromethanol. Induction of anesthesia was completed with nitrous oxide and oxygen, followed by open drop ether with oxygen insufflation. Exploration revealed two tumors, one at the organ of Zuckerkandl and the other in the epigastrium. During exploration the blood pressure was remarkably labile. Endotracheal intubation was performed during

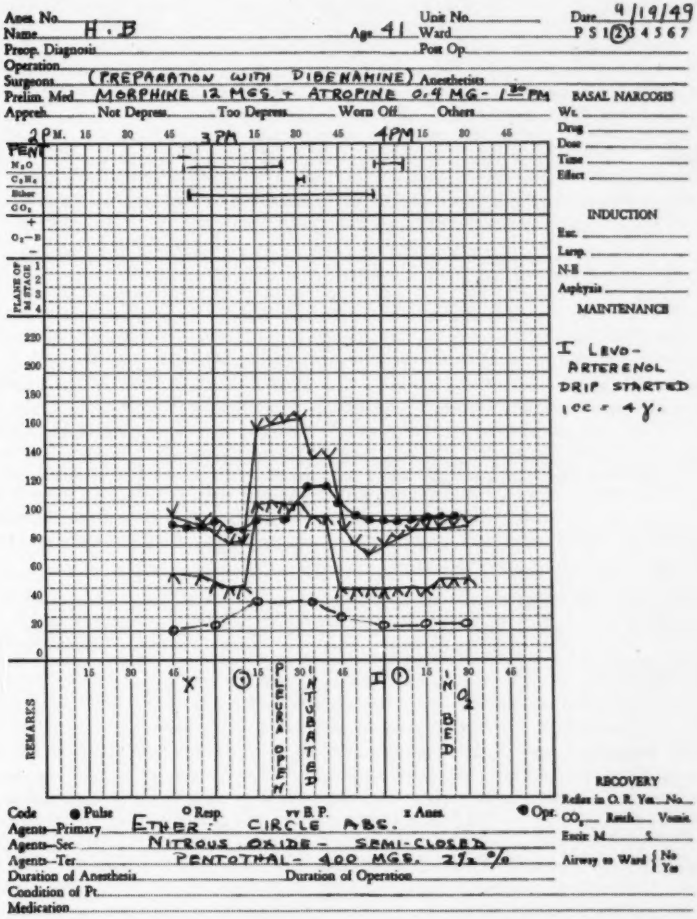


Fig. 4.—The patient had a 12 year history of paroxysms of hypertension. Exploration of the right adrenal region was noncontributory. Benzodioxan reaction was positive. Dibenamine® infusion was used 36 hours before operation. A left adrenal tumor was found at a subsequent operation and removed. Hypertensive periods were much less severe than during the other operation. Arterenol infusion was used to control hypotension during and after operation.

operation in preparation for resuscitation, since a catastrophe seemed imminent. Despite 1 mg. of ergotamine tartrate and 13 mg. of benzodioxan, cardiac arrest occurred. Resuscitation was unsuccessful.

Two previously unreported cases are next described briefly as additions to the case material in the literature.

CASE 3 (fig. 3).—M. E. was a 48 year old woman who had the classic complaints associated with pheochromocytoma for one year prior to her entry to the hospital. The blood pressure was considerably elevated during attacks. In addition there was a marked loss of body weight during the year of illness. The serum potassium was normal. On two separate occasions preparation for operation was attempted with dibenamine,® 185 mg. Operation was deferred both times because of the development of a right hemiparesis of obscure origin. Finally, operation was performed during nitrous oxide-ether anesthesia following induction with thiopental sodium. Preanesthetic medication consisted of morphine, 12 mg., and atropine, 0.3 mg. No endotracheal airway was used. A left adrenal pheochromocytoma was excised. The operation was marked by considerable variability of blood pressure. The hypotensive period was supported by a continuous intravenous drip of arterenol solution (4 mg. per liter) which was maintained for the first 24 hours after operation. Eight months after operation the patient was well symptomatically, had gained 33 pounds (15 Kg.) but remained hypertensive (200/120). The explanation for the persistence of hypertension is not clear.

CASE 4 (fig. 4).—H. B. was a 42 year old white man who was admitted with a 12 year history of profuse sweating and notable lability of blood pressure. A right lumbar exploration was carried out at another hospital without disclosing a pheochromocytoma. The anesthesia was conducted with nitrous oxide and ether, with curare added for relaxation. Preoperative preparation consisted of the administration of dibenamine,® meperidine hydrochloride (demerol®) and scopolamine. No further data are available on the course during this operation.

At the Presbyterian Hospital three months later a pheochromocytoma was found in the left adrenal gland and removed. Medication consisted of dibenamine® (5 mg. per kilogram), morphine, 12 mg., and atropine, 0.4 mg. Anesthesia was maintained with nitrous oxide and ether through an endotracheal airway, after induction with thiopental sodium (pentothal® sodium). During anesthesia the blood pressure became elevated on manipulation of the tumor and fell immediately after its removal. The resultant hypotension was corrected by an intravenous drip of arterenol, which was maintained for 48 hours after operation. Recovery was uneventful thereafter despite the occurrences of an accidental pneumothorax during the operation. There was no recurrence of hypertension eight months later.

We believe that the details of an unsuspected case of pheochromocytoma may be of interest in demonstrating the dangers of unrelated surgical procedures.

CASE 5.—M. H. was a 53 year old white woman who was admitted to the hospital the night before operation for a biopsy of a carcinoma of the breast. The information to be gained from the biopsy was concerned with the establishment of proper dosage for radiation therapy. Other than appreciable hypertension and albuminuria, there were no symptomatic complaints and no objective findings. Preanesthetic medication consisted of meperidine hydrochloride, 100 mg., and scopolamine, 0.4 mg. Light anesthesia was maintained with thiopental sodium and nitrous oxide oxygen. Cyanosis developed after some depression of respiration, with no change in the severity of the hypertension. The patient never recovered consciousness. She was treated with lanatosid-C, 1.6 mg., and carotid sinus pressure in the hope of correcting the tachycardia which developed during anesthesia. Death occurred three hours after operation with the patient in circulatory collapse, and autopsy revealed bilateral pheochromocytomas. It is possible that a correct diagnosis might have obviated this unexpected death.

COMMENT

The problems in anesthetic management during the operative treatment of pheochromocytoma are concerned largely with the physiological effects of excessive secretion of epinephrine and arterenol during excision and with the sudden circulatory depression which occurs after extirpation of the secreting mass. These will be considered in turn.

The greatest pitfall in anesthetic management is the development of anoxia, which stimulates secretion of the adrenal medulla even more than the abnormal situation already present. It is necessary to emphasize that the causes of anoxia are many during anesthesia and include excessive doses of depressing drugs, an inadequate airway, shallow ventilation, high spinal anesthesia and marked reduction in blood pressure. Anoxia in any form must be scrupulously avoided if uncontrollable tachycardia and hypertension, usually followed by circulatory collapse, are to be avoided.

The patients are peculiarly sensitive to any stress placed on circulatory dynamics. For example, they tolerate postural changes poorly. This disability has been so remarkable that anesthesia is now induced and maintained in the position of operation, usually the supine for a transperitoneal approach. The excessive quantities of circulating medullary hormone are potential causes of fatal cardiac arrhythmias in the presence of anesthetic agents likely to sensitize the myocardium. For these reasons, cyclopropane and chloroform are avoided.

There are two major surgical problems which concern the anesthesiologist. The first of these is the possibility of traumatic pneumothorax, which is dangerous when uncontrolled in the patient with pheochromocytomas. An endotracheal airway is considered an essential safeguard in all explorations. Secondly, the technical details of extirpation are of importance. The tumor must be isolated from the systemic circulation by a minimum of manipulation to avoid flooding with epinephrine and arterenol.

The selection of anesthesia is perhaps less important in some respects than meticulous attention to detail in order to avoid the physiological upsets discussed previously. Spinal anesthesia has not appeared desirable because of its potentiality for producing hypotension and the lack of protection against pneumothorax. Cyclopropane is not safe because of the large quantities of circulating epinephrine. The use of thiopental sodium and nitrous oxide oxygen is inadequate for relaxation without curare. We have been loath to use curare because of its histamine-like properties, an objection that may be more theoretical than actual.[21] A safe method which satisfies most requirements appears to be a tranquil induction with thiopental sodium followed by maintenance with ether through an endotracheal airway. There have been no serious consequences of the "sympathomimetic" qualities of ether. Premedication should not be heavy but otherwise is not of direct importance.

Intravenous drug therapy is frequently required during anesthesia and operation. Therefore, an intravenous drip is mandatory prior to the establishment of anesthesia. Benzodioxan (10 mg. in 1 cc.) is available and may be needed to reduce a paroxysmal hypertension occurring during surgical manipulation. It is rapid in action and is therefore preferable to dibenamine.® After excision of the tumor, the removal of autogenous epinephrine and arterenol may result in marked hypotension. For this phase of the procedure, arterenol (4 mg. per liter) or neo-synephrine (20 mg. per liter) infusions are utilized. These drugs are satisfactory pressor agents and have less cardiac effect than epinephrine, a desirable property. The rate of flow is adjusted to maintain a moderate hypertension during operation. It can usually be reduced postoperatively.

21. Dripps, R. D.: Personal communication to the authors.

SUMMARY

The 91 reported cases in which surgical treatment has been given for pheochromocytoma have been surveyed. The total mortality rate is 24 per cent. A brief description of the clinical picture of the disease and a summary of the important diagnostic tests are included. Suggestions for rational anesthetic management are presented, including a commentary on the supportive measures required during anesthesia and operation. The dangers of performing unrelated operative procedures on patients with pheochromocytoma are pointed out. These operations bear a mortality rate of approximately 50 per cent. Two previously unreported cases are presented.

DISCUSSION

Dr. William B. Neff, San Francisco: Surgical experiences with pheochromocytoma have been reviewed by Dr. Victor Richards. I shall limit my discussion of Dr. Apgar's informative paper to certain features in the conduct of anesthesia which we both consider important. These are avoidance of anoxia, carbon dioxide accumulation and respiratory obstruction. One of the five cases reported by Dr. Richards, which terminated fatally eight hours postoperatively, will serve to illustrate.

A. G., a 43 year old rice farmer, entered the Stanford Hospital first on Jan. 26, 1948. He complained of profuse sweating, palpitation, feeling of warmth of four years' duration with recent nervousness, fatigability and shortness of breath on exertion. He never wore an overcoat, had to sleep in a separate room at night because he felt so much warmer than the others in the house and would drive his car in the middle of winter in shirt sleeves and with open windows while others were wearing overcoats with the heater on. Physical examination showed his skin to be warm and at times drenched with sweat. His thyroid was not enlarged, there was a slight tremor, but there were no clinical signs of hyperthyroidism. His blood and urine were normal. The basal metabolism was + 57. Roentgenograms of the chest and skull and intravenous pyelograms were normal. Blood cholesterol was 150 mg. per 100 cc. The diagnosis seemed to be thyrotoxicosis, and he was treated with 200 mg. of propylthiouracil daily for seven weeks.

His drenching sweats and feeling of warmth continued. A blood iodine test was done and the value found to be 5.3 micrograms. He reentered the hospital in April 1948. His blood pressure was 170/70. The combination of profuse drenching sweats, mild hypertension, markedly elevated basal metabolism, slow pulse, normal blood iodine level and mild obesity suggested a pheochromocytoma. Exploration of the adrenals was suggested but refused by the patient.

He reentered the hospital March 7, 1949, because he perspired so profusely that he had to change clothes several times daily and was embarrassed by his condition. His ability to work had also declined. He was still overweight. His blood pressure was 180/80, and the benzodioxan test, which had been done at his local hospital, had shown a marked drop in blood pressure. Surgical intervention was decided on.

Bilateral simultaneous paravertebral incisions were elected for exposure. During induction of anesthesia the blood pressure rose to 260/160, but then it returned to its usual level. Shortly after the incisions were made the patient had an episode of mild to moderate pulmonary edema which was controlled by positive pressure through an intratracheal tube. The left adrenal was normal. The right adrenal contained a 3 by 4 cm. encapsulated tumor. Manipulation of the tumor produced paroxysmal hypertension, and while it was being dissected out his blood pressure fell to 85/70, remaining there for the remainder of the operation. Five hundred cubic centimeters of blood was given during the operation, and 1 to 2 mg of neo-synephrine was injected intravenously at frequent intervals after the blood pressure dropped. In addition 10 cc. of adrenal cortical extract were given during the latter part of the surgical procedure.

After the incisions were closed and the patient was turned onto his back, his blood pressure rose to 90/70. He returned to his room at 2:55 p. m. On arrival his blood pressure could not be obtained and he was a little cyanotic but his pulse was fairly strong. Intranasal administra-

tion of oxygen was started, and 1 cc. of 1 per cent neo-synephrine was given intravenously, without effect. Intravenous injection of 0.5 cc. of 1:1,000 epinephrine raised the blood pressure to 160/100, but it fell again rapidly. Between 3:05 and 3:45 p.m. he received a total of 3 cc. of 1:1,000 epinephrine intravenously in 0.2 cc. doses. He was also given 1 cc. of 1:500 epinephrine in oil intramuscularly. His lungs remained clear of edema, but his blood pressure fluctuated markedly. At 3:45 p.m. an infusion of 30 cc. of 1:1,000 epinephrine in 500 cc. of 5 per cent dextrose in water was started (1 mg. in 16 cc.). He was given 15 to 30 drops per minute, and his blood pressure remained around 120/75 to 100/70. However, he never regained a clear state of consciousness. At 7:30 p.m. he was catheterized and 250 cc. of clear urine obtained. A second infusion of 60 cc. of 1:1,000 epinephrine in 500 cc. of 5 per cent dextrose in water was started (1 mg. in 8 cc.). By 8 p.m. he was very restless and excitable, thrashing around and mentally confused. His blood pressure began to drop despite the epinephrine. His temperature rose rapidly to 42 C. and cyanosis appeared. Ten cubic centimeters of adrenal extract was given without effect. At 10:30 p.m. his pulse became irregular, and he died at 10:50 p.m. on March 9, 1949, the day of operation. He had received on his operative day 20 cc. of adrenal cortical extract, 500 cc. of whole blood, 1,800 cc. of saline solution, 1,000 cc. of 5 per cent dextrose in water, and 108 cc. of 1:1,000 epinephrine intravenously (supplemented with neo-synephrine at the time of operation).

Autopsy showed bilateral massive hemorrhages in the adrenals with necrosis of the medulla, partial necrosis of the adrenal cortex and severe depletion of the lipid of the adrenal cortex. There were cardiac hypertrophy, fatty degeneration and necrosis of the liver and pulmonary edema.

The cause of death seemed to be acute adrenal insufficiency and was characterized by marked hypotension and a rapidly mounting fever. The use of an adrenolytic drug during the operation might have been helpful in controlling the fluctuations in pressure at the time of operation, but certainly would not have answered the postoperative problems. More vigorous therapy with desoxycorticosterone, adrenal cortex extract and plasma might have been rewarding, in light of the recent experiences of Huggins and Scott with adrenalectomy and postoperative survival.

Additional Comment by Anesthesiologist.—It is true that the patient's blood pressure, which rose from 210/120 to 260/160 during the induction of anesthesia with nitrous oxide and ether, returned to its preanesthetic level within four minutes. There was, however, a certain degree of respiratory obstruction prior to the establishment of a patent airway by endotracheal intubation. After intubation and the handling required to turn the patient over in the prone position his blood pressure declined to 150/120 and then to 130/100. The development of secretions was troublesome from the beginning, and pulmonary edema most probably had its inception during the period of elevated blood pressure and respiratory obstruction. The edema was readily controlled by the application of positive pressure.

The blood pressure varied considerably during the protracted surgical exploration, which required one hour. During this period considerable hemorrhage was encountered, but the blood pressure dropped to dangerously low levels only when the tumor was being dissected out.

In spite of the loss of blood adequate replacement was deferred because the patient had had pulmonary edema. The anesthetist feels that adequate replacement should be made in such a case wherein pulmonary edema ceased to be a complication.

Although a patient is being anesthetized with ether vaporized with oxygen, the likelihood of anoxia and irreversible shock cannot be overlooked when a patient used to a blood pressure around 200 mm. of mercury with a wide pulse pressure is subjected to a systolic pressure of 80 mm. with a pulse pressure of 10 mm. for any length of time.

The autopsy report showing destruction of both the adrenal cortex and the medulla would indicate that the work of the anesthetist and his advisers did not result in this fatality. We are nevertheless duty bound to pay the closest attention to the dynamics of respiration and circulation in the conduct of anesthesia for this very important operation.

Dr. Alton Ochsner, New Orleans: I have listened with especial interest to this paper by Dr. Apgar, and she has presented an amazing collection of cases of this rare disease and has capably discussed the problems which arise. I should like to add the following case to this series. This case has been submitted for publication from our Clinic, and I shall cover it

only superficially and from the anesthetic point of view. This patient came to the Clinic complaining of intermittent headaches and was found to have paroxysmal hypertension. Preoperative tests included a repeatedly positive histamine test and a negative benzodioxan test; dibenamine® was not used. No special preoperative preparation was used.

As you can see on the slide, anesthesia was induced with 225 mg. of pentothal® sodium, and this was followed by a sequence of cyclopropane oxygen and ether and intubation was carried out. At the time of the exploration and massage of the left adrenal gland the blood pressure became elevated sharply from the preoperative level of 114/70 to 200/110 and remained elevated until the tumor was removed, when it fell and remained low for some time. When the patient was turned over and the right adrenal was massaged there was practically no increase in blood pressure. Assay of the tumor revealed 90 per cent arterenol. Postoperatively the blood pressure ranged from 134/80 to 102/62 and the pulse from 96 to 76. No vasopressors were required in the postoperative period, and the patient was discharged in excellent condition on the tenth postoperative day.

In accord with the report by Dr. Apgar, we believe that high spinal anesthesia is a poor choice and that anoxia must be avoided. In spite of the fact that this patient got along well, the use of cyclopropane should be avoided. We believe that pentothal® induction, with nitrous oxide, oxygen and ether and intubation, is by far the best method. Vasopressors should always be instantly available as well as agents to control serious hypertension. I should like to emphasize again the point made by Dr. Apgar that these tumors should be removed with as little massage as is compatible with surgical extirpation.

DR. VIRGINIA APGAR, New York: Dr. Ochsner is to be congratulated on his fine chart. Dr. Neff mentioned cortical extract. It has been used a great deal in the treatment of these patients, but so far as I know there is no evidence that cortical insufficiency has anything to do with this lesion. Unfortunately, there are many cases which are not reported, and it would be of real assistance if you could get them in the literature.

EFFECTS OF VAGUS SECTION WITH SUBTOTAL GASTRECTOMY AND DIVERSION OF DUODENAL SECRETIONS INTO THE TERMINAL PORTION OF THE ILEUM ON ULCER DEVELOPMENT

JAMES V. OLIVER, M.D.
CHICAGO

IT HAS previously been shown that bilateral section of the vagi did not prevent the development of the jejunal ulcer in the Mann-Williamson dog.[1] It has also been demonstrated experimentally that the presence of gastric secretion is the important factor in the development of the stomal ulcer after a Mann-Williamson operation has been performed, in so far as no ulcer will develop if all the stomach has been removed, whereas a subtotal gastrectomy leaving 25 per cent of the stomach, followed by diversion of the duodenal secretions into the terminal portion of the ileum, will result in a high incidence of stomal ulcer.[2]

Inasmuch as chronic ulcers are produced experimentally by various surgical procedures which alter the normal gastrointestinal anatomy and physiology,[3] it becomes apparent that an operative procedure which would protect an animal against the development of such an experimentally induced chronic stomal ulcer would have some clinical value in the surgical therapy of ulcer in man, in whom similar lesions occur spontaneously.[4]

This investigation was conducted to evaluate the effects of bilateral section of the vagi combined with subtotal gastrectomy on the development of the jejunal ulcer which usually follows the Mann-Williamson operation for diversion of bile, pancreatic juices and duodenal secretions into the terminal portion of the ileum.

The importance of the acid factor in the development of ulcer has been demonstrated as too definite experimentally to be disputed, and it has been demonstrated repeatedly that vagus section produces in the dog a definitive decrease in the amount of acid and in the total volume of gastric secretions. However, the failure of (1) section of the vagi alone or (2) a subtotal gastrectomy comprising three fourths of the stomach to protect against the development of the stomal ulcer in the Mann-Williamson dog, as noted in our experiments, demonstrated that the most important criterion which a satisfactory operation for the prevention of experimental ulcer must fulfil is the effectual reduction of gastric acidity.

Work performed in the Department of Surgery, University of Illinois, College of Medicine, aided by a grant from the United States Public Health Service.

1. Oliver, J. V.: Effect of Vagotomy on Development of the Mann-Williamson Ulcer in the Dog, Arch. Surg. **55**:180 (Aug.) 1947.

2. Oliver, J. V.: Effect of Gastrectomy and Diversion of Duodenal Secretions into the Terminal Portion of the Ileum on Development of Ulcer, Arch. Surg. **59**:199 (Aug.) 1949.

3. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

4. Wangensteen, O. H., and Lannin, B. G.: Criteria of an Acceptable Operation for Ulcer: Importance of Acid Factor, Arch. Surg. **44**:489 (March) 1942. Lannin, B. G.: Experimental Evaluation of a Satisfactory Operation for Ulcer, Surgery **17**:712, 1945.

In considering the physiology of gastric secretion, particularly as related to the ulcer problem, Schiffrin and Ivy [5] have discussed the fundamentals of the normal physiology of gastric secretory response, which is divided into the continuous or interdigestive phase of secretion and the digestive phase. During the interdigestive period of secretion the empty or fasting stomach continues to secrete from 30 to 60 cc. of gastric juice per hour. Although the mechanism concerned in its stimulation is obscure, it is believed to be due to histamine liberated by the irritated gastric mucosa. The digestive phase of secretion is the gastric secretory response to a meal and is divided into a cephalic phase, gastric phase and intestinal phase, each phase denoting the region in which the stimuli are acting to excite gastric digestion.

The cephalic phase, which is provoked by stimuli such as thought, smell, sight and taste of foods, acts in the presence of appetite through either conditioned (learned) or unconditioned (unlearned) reflexes. The vagi are the efferent nerves in the cephalic phase of digestive gastric secretory response since their section will abolish this phase. The juice in the cephalic phase is highly acid and has considerable peptic activity and the amount secreted in man is variably estimated at 45 to 60 per cent of the total.[6] The gastric phase of gastric secretory response is stimulated by mechanical distention of the stomach caused by foods and by secretogogues which are present in foods or arise as products of digestion. The secretogogues may act as such or through the liberation of a gastric hormone. The vagi, which are preganglionic fibers, are not necessary for this phase of gastric secretion. The volume of the gastric phase secretion is variable and dependent on the length of time food is in the stomach, regurgitation from the intestines, types of foods ingested and the distention produced by various foods. There are no satisfactory data regarding the volume since no definite demarcation denotes the cessation of cephalic secretion and the beginning of gastric phase secretion. The intestinal phase of gastric secretory response is provoked by secretogogues acting in the intestine.

The total volume of gastric secretion is estimated at from 2 to 3 liters per day, dependent on types of food ingested. Proteins are more potent stimulants of gastric secretion than are carbohydrates.

Since vagus section will abolish the cephalic phase of gastric secretion, its value in conjunction with other operative procedures is thus considered.[7] Its ultimate value will depend on the preoperative importance of the cephalic phase or vagal activity. The prolonged presence of food in the stomach induced by atonicity of gastric musculature following vagotomy, thus increasing emptying time, stimulates the gastric phase of secretory response and may defeat the effects of vagectomy by stimulating the gastric phase of secretory response.

The literature on section of the vagi in the treatment of duodenal ulcers has been reviewed by Hartzell,[8] who found that in dogs the volume and acidity of the gastric secretions in response to cephalic stimulation were markedly reduced when the vagi were sectioned above the diaphragm.

5. Schiffrin, M. J., and Ivy, A. C.: Physiology of Gastric Secretion, Particularly as Related to the Ulcer Problem, Arch. Surg. **44**:399 (March) 1942.

6. Wakerlin, G. E.: Personal communication to the author.

7. Neuwelt, F.; Medoff, J.; Patedjl, J., and Necheles, H.: Study of Functions of Stomach Following Pyloric Obstruction and Gastro-Enterostomy, Am. J. Digest. Dis. **8**:310, 1941.

8. Hartzell, J. B.: Effect of Section of Vagus Nerves on Gastric Acidity, Am. J. Physiol. **91**:162, 1929.

Numerous investigators have reported on the decrease of gastric secretory response in both volume and degree of acidity following section of the vagi.[9] In dogs, gastroenterostomy alone cannot be relied on to reduce gastric secretory response as effectively as gastric resection. Gastroenterostomy is contraindicated in true hypersecretion since it does not attack the cause of secretion and exposes the susceptible jejunum to proteolytic action of gastric juice.[10] Subtotal gastrectomy, however, permits regurgitation more readily, reduces the emptying time of gastric contents and obliterates the humoral mechanism of gastric secretion, and, in addition, a portion of the acid-bearing gastric mucosa is excised.

Lewis [11] excised the mucosa of the pyloric antrum and noted a decrease in the volume of gastric secretion, and he stressed the importance of the pylorus in gastric secretion.

Evidence submitted by Ivy [12] indicates that while the pyloric mucosa is not the sole cause of humoral secretion its contribution is significant. The extent to which partial gastrectomy will reduce the gastric phase of secretory response [13] depends on (1) the extent of acid-bearing portion removed, (2) the degree of hypertrophy and hyperplasia of gastric remnant which follows and (3) the size and character of the meal.

Heuer,[14] in a study of the effects of gastric acidity following gastroenterostomy and gastric resection for peptic ulcer, noted that of the 75 patients on whom gastroenterostomy had been performed only 75 per cent had good clinical results after six to 10 years. Of the 88 cases in which a minimal resection had been performed, good results were obtained in over 90 per cent. Obviously, extirpation of the pylorus with subsequent reduction of gastric secretory response sufficed to increase the over-all percentage of good results in the latter group.

Wangensteen,[15] in a series of 31 cases in which a gastric resection comprising less than one half of the stomach was performed, noted anacidity in only 6.4 per cent, with good results in 90.3 per cent of the total. Of 11 patients in another series, however, in whom a subtotal gastrectomy comprising three fourths of the stomach was performed, 72.7 per cent showed postoperative anacidity, with good results in all 11 (100 per cent). In discussing the clinical aspects of the ulcer problem, Wangensteen laid down certain criteria which a satisfactory operation for ulcer must fulfil, as follows: (1) extensive gastric resection; (2) short afferent loop and gastrojejunostomy; (3) sacrifice of major vagal branches; (4) decreased emptying time, and (5) achlorhydria to maximal stimulation.

---

9. Dragstedt, L. R.: Vagotomy for Gastroduodenal Ulcer, Ann. Surg. **122**:973, 1945.

10. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer: Experimental Studies, Surg., Gynec. & Obst. **55**:265, 1932.

11. Lewis, E. B.: Acidity of Gastric Contents After Excision of the Antral Mucosa, Surgery **4**:692, 1938.

12. Ivy, A. C.: The Mechanisms of Gastric Secretion, Surgery **10**:861, 1941.

13. Connell, F. G.: Resection of the Fundus of the Stomach for Peptic Ulcer, Ann. Surg. **96**:200, 1932.

14. Heuer, G. J., and Holman, C. W.: Effect on Gastric Acidity of Gastro-Enterostomy and Gastric Resection for Peptic Ulcer, Ann. Surg. **118**:551, 1943.

15. Wangensteen, O. H.: Clinical Aspects of the Ulcer Problem with Special Reference to Definition of Criteria of Suitable Operation: Importance of a Short Afferent Loop, and Results of Operation, Minnesota Med. **27**:714, 1944.

METHODS OF EXPERIMENTAL PROCEDURE

This investigation was divided into three experimental procedures. All animals in all three groups were first subjected to a bilateral supradiaphragmatic vagus nerve resection. In dogs, it is practically impossible to perform a subdiaphragmatic vagus resection with any assurance of completeness, since the esophagus lacks mobility at this point and the vagus nerves fan out above the diaphragmatic esophageal hiatus.

In the first group of experimental animals, a subtotal gastrectomy was performed comprising three fourths of the stomach, followed by diversion of the bile, pancreatic juices and duodenal secretions into the terminal portion of the ileum 25 cm. from the ileocecal junction, after the method of Mann and Williamson. The second experimental group underwent a gastric resection comprising one half of the stomach, followed by diversion of the duodenal contents into the terminal portion of the ileum. The third group were subjected to a minimal gastric resection comprising one fourth of the stomach, followed by shunting of the duodenal secretions into the terminal portion of the ileum. The animals in all groups were permitted to survive their life span after the operative procedures.

On arrival, all animals were quarantined for a period of 10 days and placed on a stock diet of dog chow and water. Preoperatively no therapeutic or dietary measures were utilized to condition the animal. Postoperatively the diet consisted of milk for three days, after which they were fed a ration of milk, bread, dog food and dog chow. We used this improved diet because the experimental animals experienced great difficulty in maintaining their nutritional state on a diet of dog chow alone and perished within too short a period (usually two weeks) for the results to be of statistical significance. It is manifest that an experimental animal which has been subjected to a bilateral vagus section, subtotal gastrectomy, gastrojejunostomy and finally diversion of the duodenal contents drained into the terminal portion of the ileum is in dire need of all possible nutritional factors to prevent early death. Other than a modification of the diet, no other medication or therapeutic measures were instituted postoperatively. Animals surviving less than 30 days were discarded in the evaluation of the results of the experiments since it is obvious that these animals had succumbed too soon after the last operation to be used statistically; many of them died at operation or shortly thereafter.

Series A. Bilateral Vagus Nerve Section with Subtotal (Three-Fourths) Gastric Resection and Diversion of the Duodenal Secretions into the Terminal Portion of the Ileum.—The first series comprises a group of experimental animals which were first subjected to a bilateral vagus nerve section performed as follows: With the animals under morphine and intraperitoneal pentobarbital sodium anesthesia with positive pulmonary pressure, the thorax was entered through an incision in the left sixth intercostal space. The lower part of the esophagus was delivered into the wound, and the right and left vagi including all interlacing fibers were resected. The completeness of the vagus section was further insured by incising the serosa enveloping the esophagus with a circular incision down to the muscularis.

After a short recovery period, the vagectomized animals were then subjected to the second operation, a subtotal (three-fourths) gastrectomy with intestinal continuity restored by an end to side gastrojejunostomy. All animals surviving the vagus section and subtotal gastric resection were later subjected to the Mann-Williamson operation for shunting the duodenal contents, bile and pancreatic juice into the terminal portion of the ileum, performed as follows: The efferent limb of the gastrojejunostomy was transected at the duodenojejunal flexure. The distal limb of the jejunum was inverted and closed and the proximal limb sutured end to side into the terminal portion of the ileum 25 cm. from the ileocecal junction (fig. 1).

In this series, six animals survived the third or final operation 30 days or more; the experimental data herein analyzed are derived only from this surviving group.

Series B. Bilateral Vagus Nerve Resection with Subtotal (One-Half) Gastrectomy and Diversion of the Duodenal Contents into the Terminal Portion of the Ileum.—In this second experimental group all animals were subjected to the three operations as previously described for the group in series A, viz., bilateral vagectomy, subtotal gastrectomy and internal duodenal drainage, except that the animals in this group were subjected to a gastric resection comprising the pylorus and one half of the stomach, as contrasted with the more extensive gastrectomy (three-fourths) for the animals in series A (fig. 2).

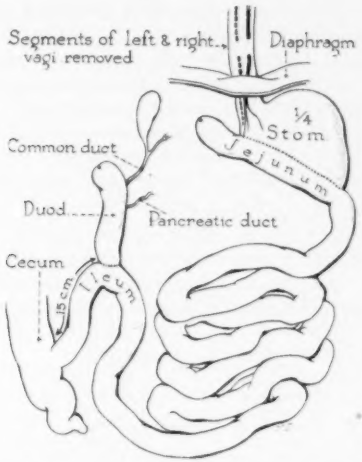


Fig. 1.—Bilateral supradiaphragmatic section of the vagus nerve was performed, followed by partial "subtotal" gastrectomy (leaving 25 per cent of the stomach), with anastomosis of the stomach to the jejunum just distal to the ligament of Trietz. A Mann-Williamson operation was performed later, the distal end of the duodenum being transplanted into the terminal portion of the ileum. (For results regarding ulcer formation, see table 1, series A.)

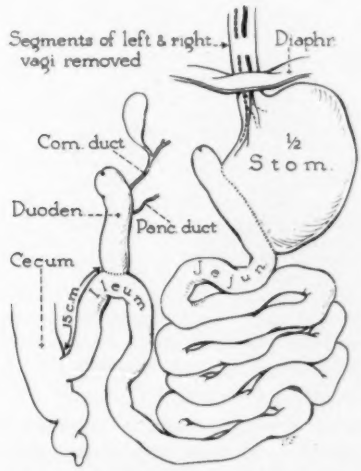


Fig. 2.—Bilateral supradiaphragmatic section of the vagus nerve was performed, followed by a gastric resection comprising the pylorus and 50 per cent of the stomach, with anastomosis of the stomach to the jejunum. At a subsequent stage a Mann-Williamson operation, with anastomosis of the distal end of the duodenum to the ileum, was performed. (For results regarding ulcer formation, see table 2, series B.)

Six animals survived the third or final operation 30 days or more, and the data herein analyzed are derived from this surviving group.

Series C. Supradiaphragmatic Bilateral Vagus Nerve Resection Followed by a Gastric (One-Fourth) Resection with Diversion of the Duodenal Contents into the Terminal Portion of the Ileum.—The third group of animals were subjected to the same three operations as those performed on the animals in the previous two groups except that the gastric resection for this group was minimal and comprised only one fourth of the stomach (fig. 3). Data on only those animals which survived the third operation 30 days or more are analyzed. The survivors in this group number 10 animals.

RESULTS

Series A.—In the six experimental animals analyzed in this series, death occurred 34, 44, 45, 53, 65 and 71 days respectively after the third (Mann-Williamson) operation. At their death following the three operations, all animals

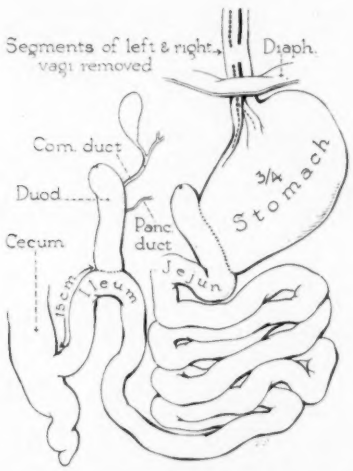


Fig. 3.—Bilateral supradiaphragmatic section of the vagus nerve was performed, followed by a minimal gastrectomy comprising only the pyloric antrum, with intestinal continuity restored by an end to side gastrojejunostomy. Later, a Mann-Williamson operation for diversion of the duodenal secretions, bile and pancreatic juice into the terminal portion of the ileum was performed. (For results regarding ulcer formation, see table 3, series C.)

which survived the last (Mann-Williamson) operation 30 days or more exhibited evidence of severe nutritional failure, with weight losses averaging 50 per cent of their preoperative body weight (see table 1).

At necropsy no stomal or jejunal ulcer was noted in any of the animals which died, and neither was there any evidence of a healed ulcer. Death in all six animals was due to inanition. The stomachs of all the animals manifested marked dilatation (up to 400 cc. capacity), extreme thinning of the wall with atonicity and flattening of the rugal pattern. The jejunum in these animals did not show any noteworthy changes. The stomas in all animals appeared adequate and presented no noteworthy changes.

Series B.—In this group, as previously explained, bilateral vagus nerve resection was performed first, followed by a gastrectomy comprising one half of the stomach with subsequent diversion of the duodenal contents into the terminal portion of the ileum. At their death, all animals which survived the third operation 30 days or more showed marked evidence of nutritional imbalance, and some were extremely emaciated, with weight losses also ranging from 40 to 50 per cent of their preoperative body weight (see table 2).

In this series of six experimental animals which survived the last operation 30 days or more, death occurred 32, 36, 38, 44, 54, and 61 days, respectively, after operation. At necropsy on the six animals which died no stomal ulcer was noted,

TABLE 1.—*Series A. Bilateral Vagus Nerve Resection Followed by Subtotal (Three-Fourths) Gastrectomy with Diversions of Duodenal Secretions into the Terminal Ileum*

Dog No.	Weight, Lb.	Date of Mann-Williamson Operation	Date of Death	Survival Time, Days	Weight Loss, Lb.	Comment
1	15	4/20/48	6/ 3/48	44	7	No ulcer apparent; marked inanition
2	15	4/20/48	6/24/48	65	7½	No stomal ulcer; stomach atonic and dilated
3	27	5/25/48	7/ 9/48	45	14	No stomal ulcer; stomach dilated
4	31	5/ 4/48	6/14/48	41	17½	No stomal ulcer; stomach dilated to 400 cc., wall thin and atonic
5	25	6/30/48	9/ 9/48	71	9	No stomal ulcer
6	32	8/ 3/48	9/25/48	53	18	No stomal ulcer

TABLE 2.—*Series B. Bilateral Vagus Resection Followed by Subtotal (One-Half) Gastrectomy with Duodenal Contents Shunted into the Terminal Ileum*

Dog No.	Weight, Lb.	Date of Mann-Williamson Operation	Date of Death	Survival Time, Days	Weight Loss, Lb.	Comment
7	28	9/10/48	11/ 2/48	54	14¾	No stomal ulcer
8	16	10/28/48	12/11/48	44	7	No stomal ulcer
9	25	11/ 2/48	12/10/48	38	12	No stomal ulcer
10	28½	1/ 8/49	3/ 9/49	61	13½	No stomal ulcer
11	31	2/11/49	3/19/49	36	15	No stomal ulcer
12	22	3/18/49	4/19/49	32	10	No stomal ulcer

and neither was there any evidence of a healed ulcer. Death in all instances was due to nutritional failure. The remaining portion of the stomachs in all animals in this series also showed dilatation and atonicity, with obliteration of the rugal patterns. The stomas in all dogs evidenced no noteworthy changes, and the jejunum in all animals was normal.

Series C.—The results analyzed in this series are derived from those animals which were subjected to a bilateral vagus nerve resction, with subsequent diversion of the duodenal contents into the terminal portion of the ileum. Of the 11 animals which survived the third (Mann-Williamson) operation 30 days or more, death occurred in nine animals in 31, 36, 46, 63, 88, 91, 94, 113 and 117 days respectively. One animal was killed 185 days after operation. After the third (Mann-Williamson) operation, this particular animal was placed on a diet consisting of milk, cooked meat, bread, dog food with supplemental raw liver and pancreas. At the time of

death the animal was in a fairly satisfactory nutritional state, and it is possible that with this added variation in diet he would have lived indefinitely. The value of a highly nutritious diet, as described above, in maintaining the nutritional state of the experimental animals, is obvious when a comparison is made of the longevity in this animal and the survival time (average, 60 days) of the remainder of the animals used in these experiments. At necropsy none of the 11 animals which survived the final operation 30 days or more showed evidence of a stomal or jejunal ulcer and neither was there any evidence of a healed ulcer. Death in eight animals was due to inanition. One animal died of intussusception of the afferent limb of the gastrojejunostomy, and one was killed, as previously explained. Inspection of the stoma, jejunum and stomach of the survivors in this group showed no noteworthy anatomicopathological changes other than dilatation of the stomach, with minimal compensatory dilatation of the gastrojejunal stoma.

TABLE 3.—*Series C. Bilateral Vagus Resection Followed by Gastric Resection (One-Fourth) with Duodenal Contents Shunted into the Terminal Ileum*

Dog No.	Weight, Lb.	Date of Mann-Williamson Operation	Date of Death	Survival Time, Days	Weight Loss, Lb.	Comment
13	20½	5/12/49	6/13/49	31	9	No stomal ulcer
14	22½	6/ 9/49	7/15/49	36	10½	No stomal ulcer
15	26	5/22/49	7/ 7/49	46	12	No stomal ulcer
16	20	8/ 4/49	10/ 7/49	63	8½	No stomal ulcer
17	21	6/22/49	Killed	185	4½	No stomal ulcer
18	15¾	1/30/50	4/21/50	91	6¾	No stomal ulcer
19	18½	2/ 3/50	5/ 8/50	94	8	No stomal ulcer
20	19	4/13/50	8/ 8/50	117	6	Died of intussusception; no stomal ulcer noted
21	17	4/23/50	7/20/50	88	6¾	No stomal ulcer
22	20	4/23/50	7/31/50	99	8¾	No stomal ulcer
23	16	6/ 1/50	9/21/50	113	8½	No stomal ulcer
24	19	9/ 6/50	Alive on Oct. 10, 1950			

COMMENT

Studies on the effect of bilateral vagus nerve resection with subsequent gastric resection, however minimal, indicate its efficacy in preventing the development of the stomal ulcer which usually follows gastrojejunostomy with diversion of the duodenal secretions, bile and pancreatic juice into the terminal portion of the ileum.

In one of the previous experiments it was noted that even though complete vagotomy abolished the cephalic phase of gastric secretion, all animals developed stomal ulcers at the site of gastrojejunostomy after diversion of the duodenal contents into the terminal portion of the ileum according to the method of Mann and Williamson. In another study, with diversion of duodenal secretion into the terminal portion of the ileum but without vagus section, we noted that if at least 25 per cent of the stomach remained stomal ulcers would develop at the gastrojejunostomy line of anastomosis after diversion of the duodenal secretions into the terminal portion of the ileum, as previously explained. In the former instance there is partial suppression of gastric secretory function by obliteration of the cephalic phase of gastric secretion (by vagus section). In the latter instance there is also suppression of a portion of gastric secretory function by obliteration of the pyloric or gastric phase of gastric secretion. Obliteration of the middle two quarters of

the stomach, with removal of much of the acid parietal cells found in the fundus or body of the stomach, did not prevent development of the stomal ulcer. Can the failure of either of the two procedures, vagus resection with subsequent suppression of cephalic secretion alone or extirpation of that portion of the stomach which initiates the gastric phase of gastric secretory function (pyloric antrum), be attributed to failure of each procedure alone to produce the degree of hypoacidity necessary to prevent stomal ulcer or can the stomal ulcer be attributed to jejunal susceptibility to acid even in minimal amounts and decreased degree of acidity?

The animals in series A of the present experiment had three fourths of their stomach removed, this amount of stomach representing the major portion of the acid-secreting mucosa, whereas the animals in series C had only one fourth of their stomachs removed and the major portion of the acid-bearing mucosa left; yet neither group developed stomal ulcers.

We have ample clinical and experimental evidence to support the theory of increased jejunal susceptibility to acid secretion (however minimal in amount) in hemorrhage and perforation of the ileum in a case of Meckel's diverticulum containing gastric mucosa. It is obvious that complete vagus nerve resection, with suppression of the cephalic phase of gastric secretion, accompanied with extirpation of the antrum of the stomach and consequent suppression of the gastric phase of secretory response, will result in the necessary degree of gastric anacidity to protect the jejunum, however susceptible to acid gastric juice, and prevent the development of a stomal or jejunal ulcer.

SUMMARY

Of six animals in series A in which a bilateral supradiaphragmatic resection of the vagi was followed by removal of three fourths of the stomach and restoration of intestinal continuity by means of an end to side gastrojejunostomy and diversion of the duodenal secretions into the terminal portion of the ileum, none developed stomal ulcers and all died of inanition.

Further data on six animals in series B in which the vagus resection was followed by a subtotal (one-half) gastrectomy and subsequent Mann-Williamson operation revealed that none of the animals exhibited jejunal ulcer and all succumbed to the effects of inanition.

In the final group of 12 animals in series C in which the vagus resection was followed by a minimal gastric resection (one-fourth) comprising only the pyloric antrum, with diversion of the duodenal secretions into the terminal portion of the ileum, nine animals died of inanition and one died of intussusception, and on necropsy none evidenced a stomal or jejunal ulcer. One animal which was killed after 185 days did not show a stomal ulcer at necropsy. One is still alive more than 30 days after the final operation.

CONCLUSIONS

From this data it is concluded that in the dog bilateral supradiaphragmatic resection of the vagi plus extirpation of the pyloric antrum will adequately suppress gastric secretory response and result in the necessary degree of gastric anacidity to prevent the development of the stomal ulcer which usually results after gastrojejunostomy and diversion of the duodenal secretions, bile and pancreatic juice into the terminal portion of the ileum according to the method of Mann and Williamson. Neither vagotomy nor antral resection alone prevents such ulcers.

9 South Kedzie Avenue.

EFFECT OF VAGOTOMY AND SUBTOTAL GASTRIC RESECTION ON THE SECRETION OF MUCIN IN THE HUMAN STOMACH

GEORGE B. JERZY GLASS, M.D.
WALTER L. MERSHEIMER, M.D.
AND
CHESTER S. SVIGALS, M.D.
NEW YORK

CONSIDERABLE work has been done studying the effects of subtotal gastric resection on the secretion of acid and pepsin in the human stomach, and the results of these studies are generally known. Attention has been directed in recent years to the effects of bilateral vagotomy in human beings on the secretion of hydrochloric acid,[1] especially after the development of the insulin test for evaluation of the continuity of the vagus nerves.[2] The effect of combined procedures (vagotomy

From the departments of medicine and surgery of the New York Medical College, Flower and Fifth Avenue Hospitals.

1. Dragstedt, L. R., and Owens, F. M., Jr.: Supradiaphragmatic Section of the Vagus Nerves in the Treatment of Duodenal and Gastric Ulcers, Proc. Soc. Exper. Biol. & Med. **53**: 152, 1943. Dragstedt, L. R.; Palmer, W. L.; Schafer, P. W., and Hodges, P. C.: Supra-Diaphragmatic Section of the Vagus Nerves in the Treatment of Duodenal and Gastric Ulcers, Gastroenterology **3**:450, 1944. Weinstein, V. A.; Colp, R.; Hollander, F., and Jemerin, E. E.: Vagotomy in the Therapy of Peptic Ulcer, Surg., Gynec. & Obst. **79**:297, 1944. Moore, F. D.; Chapman, W. P.; Schulz, M. D., and Jones, C. M.: Resection of the Vagus Nerves in Peptic Ulcer: Physiologic Effects and Clinical Results, with a Report of 2 Years' Experience, J. A. M. A. **133**:741 (March 15) 1947. Moses, W. R.: Critique on Vagotomy, New England J. Med. **237**:603, 1947. Woodward, E. R.; Dragstedt, L. R.; Tovee, E. B.; Obertelman, H. A., Jr., and Neal, W. B., Jr.: Quantitative Study of Effect of Vagotomy on Gastric Secretion in the Dog, Proc. Soc. Exper. Biol. & Med. **67**:350, 1948. Appleby, L. H.: An Assessment of the Results of Vagotomy (Based upon Personal Experience of 66 Cases), Canad. M. A. J. **59**:58, 1948. Stein, I. F., Jr., and Meyer, K. A.: Studies on Vagotomy in the Treatment of Peptic Ulcer: III. Physiological Aspect, Surg., Gynec. & Obst. **87**:188, 1948. Alvarez, W. C.: Sixty Years of Vagotomy: A Review of Some Two Hundred Articles, Gastroenterology **10**:413, 1948. Grimson, K. S.; Rundles, R. W.; Baylin, G. J.; Taylor, H. M., and Lindberg, E. J.: Vagotomy: Clinical Experiences During 4 Years, J. A. M. A. **139**:508 (Feb. 19) 1949. Winkelstein, A., and others, in discussion on Grimson, K. S.; Ruffin, J. M., and Hollander, F.: Symposium on Peptic Ulcer with Particular Reference to Vagotomy, Gastroenterology **7**:615, 1946. Orr, I., and others: Discussion on Vagal Resection for Peptic Ulcer, Proc. Roy. Soc. Med. **41**:639, 1948.

2. Jemerin, E. E.; Hollander, F., and Weinstein, V. A.: A Comparison of Insulin and Food as Stimuli for the Differentiation of Vagal and Non-Vagal Gastric Pouches, Gastroenterology **1**:500, 1943. Hollander, F.: Insulin Test for Presence of Intact Nerve Fibers After Vagal Operations for Peptic Ulcer, ibid. **7**:607, 1946. Hollander, F.: Laboratory Procedures in the Study of Vagotomy (with Particular Reference to the Insulin Test), ibid. **11**:419, 1948. Weinstein, V. A.; Hollander, F.; Lauber, F. V., and Colp, R.: Correlation of Insulin Test Studies and Clinical Results in a Series of Peptic Ulcer Cases Treated by Vagotomy, ibid. **14**:214, 1950.

plus partial gastric resection) also has been studied,[3] as well as the effect of these procedures on the secretion of gastric pepsin.[4]

The effect of these operative procedures on the secretion of gastric mucin and its various fractions is practically unknown. The fragmentary data available are based exclusively on the crude visual estimation of gastric mucin, by direct observation through gastric fistula,[5] or during gastroscopy,[6] either in the gastric juice or on the surface of the gastric mucosa. In view of the significance of the mucus in protection of the gastric mucosa from peptic digestion and trauma,[7] this problem deserves a careful study.[8]

The introduction of a method for the quantitative determination of gastric mucin and its fractions[9] enabled a more detailed approach to this problem. The mucin occurs in two grossly different forms, i. e., (*a*) as a visible surface epithelium mucus, which forms the protective layer on the gastric mucus and the small particles of which are found in the form of shreds and lumps in the aspirated gastric juice,

3. (*a*) Wilhelmj, C. M.; McCarthy, H. H., and Hill, F. C.: Gastric Acidity Following Partial Gastrectomy and Vagotomy, Am. J. Physiol. **117**:533, 1936. (*b*) Winkelstein, A., and Berg, A. A.: Vagotomy Plus Partial Gastrectomy for Duodenal Ulcer, Am. J. Digest. Dis. **5**:497, 1938. (*c*) McCarthy, H. H.: The Effect of Vagotomy and Partial Gastrectomy on Gastric Acidity: Effect of Stimulation of the Psychic Phase in the Presence of Tenth-Normal Hydrochloric Acid in the Stomach, Proc. Staff Meet., Mayo Clin. **21**:142, 1946. (*d*) Colp, R.; Klingenstein, P.; Druckerman, L. J., and Weinstein, V. A.: A Comparative Study of Subtotal Gastrectomy With and Without Vagotomy, Ann. Surg. **128**:470, 1948. (*e*) Santy, P.; Marion, P.; Meley, J., and Schmuck, S.: Gastric Secretion After Subtotal Gastrectomy for Ulcer: Comparative Study of Reduction of Secretion After Gastrectomy and After Vagotomy, Lyon chir. **43**:60, 1948.

4. Schoen, A. M.: The Effect of Vagotomy on Human Gastric Secretion, in Bockus, H. L.: Postgraduate Gastroenterology, Philadelphia, W. B. Saunders Company, 1950, p. 168.

5. Wolf, S., and Andrus, W. DeW.: The Effect of Vagotomy on Gastric Function, Gastroenterology **8**:429, 1947.

6. (*a*) Wolff, R.: The Gastroscopic Appearance of Gastric Mucosa Before and After Vagotomy, Gastroenterology **10**:231, 1948. (*b*) Asher, L. M.: The Gastric Mucosa After Vagotomy for Peptic Ulcer: A Gastroscopic Study, ibid. **11**:303, 1948. (*c*) Schindler, R., and Giere, N.: Gastric Surgery and Gastroscopy: Differential Diagnosis of Benign and Malignant Lesions; Operability of Tumors as Determined by Gastroscopy; Early Diagnosis of Gastric Carcinoma; Postoperative Stomach, Arch. Surg. **35**:712 (Oct.) 1937. Schindler, R.: Gastroscopic Observations in Resected Stomachs, Am. J. Digest. Dis. **7**:505, 1940. (*d*) Moersch, H. J., and Walters, M.: Gastroscopic Observations in Cases of Gastric Distress Following Operations on the Stomach, Surg., Gynec. & Obst. **71**:129, 1940. (*e*) Paulson, M., and Gladsden, E. S.: Partial Gastrectomy: The Clinical Gastroscopic and Radiological Considerations, Gastroenterology **10**:970, 1948. (*f*) Palmer, E. D.: Observations on the Etiology of Postoperative Gastritis, ibid. **10**:671, 1948. (*g*) Gray, H. K.; Meyers W. C., and Doherty, M. B.: Postgastrectomy Gastritis, S. Clin. North America **28**:965, 1948.

7. Wolf, S., and Wolff, H. G.: Human Gastric Function: An Experimental Study of a Man and His Stomach, ed. 2, New York, Oxford University Press, 1947, pp. 262.

8. Bockus, H. L.: The Present Status of Vagotomy in the Treatment of Peptic Ulcer: The Internist's Viewpoint, in Bockus, H. L.: Postgraduate Gastroenterology, Philadelphia, W. B. Saunders Company, 1950, p. 192.

9. Glass, G. B. J., and Boyd, L. J.: The 3 Main Components of the Human Gastric Mucin: Dissolved Mucoproteose, Dissolved Mucoprotein and Mucoid of the Gastric Visible Mucus: I. Differentiation; Some Physical and Chemical Characteristics; Classification, Gastroenterology **12**:821, 1949; II. Method for Separation and Quantitative Determination of Each Mucous Component of the Gastric Content, ibid. **12**:835, 1949; III. Preliminary Data on Physiological and Clinical Significance of Separate Quantitative Determination of the Dissolved Mucoproteose and Dissolved Mucoprotein in the Gastric Juice of Man, ibid. **12**:849, 1949.

and (*b*) as mucin dissolved in gastric juice, which provides the feature of viscosity but which cannot be separated from the total secretions (neither by filtration nor by centrifugation) except by chemical methods of separation.

The dissolved mucin is also a heterogenous mixture of at least two chemically different components [10]; one of these, called the "dissolved gastric mucoproteose," is the dissolution and degradation product of the surface epithelium mucus, and the other one, called "dissolved gastric mucoprotein" and, more recently, "glandular mucoprotein," is apparently the secretory product of mucous cells of the gastric glands. Also, it has been shown recently that the glandular mucoprotein, the mucous substance of glandular origin, is the only mucous component strongly influenced by vagal impulses.[11] Similarly to the way in which gastric pepsin increases [12] its concentration rises sharply in the intact stomach after intravenous administration of insulin.

Subsequent studies [13] have indicated that the response of gastric dissolved mucoprotein to insulin was abolished in the vagotomized stomach; a test to determine whether this occurred was therefore proposed as an addition to Hollander's test. It has been found, moreover, that the positive response of mucoprotein to insulin is not changed in the partially resected stomach.[13a] This fact distinguishes the mucoprotein response from the acid response. The present studies were undertaken to obtain further details of the effects of either vagotomy or partial gastrectomy alone or of the combined procedures on the secretion of gastric mucin and its fractions in the human stomach.

MATERIAL AND METHODS

Thirty-five patients were studied, of whom 31 had peptic ulcer, two had gastric carcinoma, one had gastric lymphosarcoma and one had benign polyposis of the stomach. The ulcer was duodenal in 22 cases, pyloric in five cases and gastric in three cases, and in one case it was located on the stoma of a gastrojejunal anastomosis. Twenty-two of the cases were studied both before and after operation. In each case the studies were done under fasting conditions and after insulin stimulation, which represents the most comprehensive stimulus for all gastric secretory products.

Fifty-seven insulin tests were performed altogether, and the technic adopted was described in greater detail elsewhere.[11a] The stomach, under fasting conditions, was emptied through a

10. (*a*) Glass, G. B. J.; Boyd, L. J.; Heisler, A., and Drekter, I. J.: Studies on Dissolved Mucin of the Gastric Juice: III. Heterogeneity of the Gastric Dissolved Mucin and Its Differentiation and Separation into 2 Main Fractions; Dissolved Mucoproteose and Dissolved Mucoprotein, Bull. New York M. Coll. **11**:8, 1948. (*b*) Glass, G. B. J., and Boyd, L. J.: Studies on Dissolved Mucin of the Gastric Juice: IV. Relationship of the Mucoid of the Visible Gastric Mucus, Its Split Products, and the Salivary Mucin to the Dissolved Gastric Mucoproteose and Mucoprotein of the Gastric Juice, ibid. **12**:1, 1949. (*c*) Glass and Boyd.[9] (*d*) Glass, G. B. J.; Boyd, L. J., and Svigals, C. S.: The Absence of Glandular Mucoprotein and the Presence of Mucoproteose from Surface Epithelium in the Gastric Juice of Patients with Pernicious Anemia, Bull. New York M. Coll. **13**:15, 1950.

11. (*a*) Glass, G. B. J., and Boyd, L. J.: Response of Gastric-Dissolved Mucoprotein to Insulin: A New Test for Evaluation of Secretory Status of Fundal Glands and Integrity of Nervous Pathways to the Stomach, Bull. New York Acad. Med. **25**:459, 1949. (*b*) Glass, G. B. J., and Boyd, L. J.: Patterns of Response of Gastric Mucoprotein and Acid to Insulin: Correlation with the Underlying Disease in the Non-Operated Stomach of Man, Gastroenterology **15**:438, 1950. Glass and Boyd.[9]

12. Glass, G. B. J.; Pugh, B. L., and Wolf, S.: Correlation of Acid, Pepsin and Mucoprotein Secretion by Gastric Glands, J. Appl. Physiol. **2**:571, 1950.

13. Glass, G. B. J.: New Physiological and Clinical Studies on the Secretion of Mucin in the Human Stomach, Rev. Gastroenterol. **16**:687, 1949. Glass and Boyd, footnotes 9 and 11 *a*.

Levin tube as completely as possible, and 20 minutes later the second fasting specimen was obtained by complete aspiration. Sixteen units of regular insulin was given intravenously, after which the stomach was emptied as completely as possible 20, 40 and 60 minutes after injection. Each of the five specimens was tested for free and total acidity by titration with twentieth-normal sodium hydroxide in the presence of Toepfer's reagent and phenolphthalein. The mucoprotein and mucoproteose fractions of gastric mucin were determined by the colorimetric tyrosine method of Jerzy Glass and Boyd [9] and with its volumetric modification [11b] in case of excessive contamination of gastric contents with food or bile. This volumetric modification is suitable for the study of highly contaminated gastric contents, which often are present after gastrectomy or vagotomy. A study of the surface epithelium mucus was not done, since only a small fraction of this component can be obtained by aspiration of the contents of the stomach, most of it remaining adherent to the gastric wall and escaping quantitative determination.

The volume of the gastric juice was determined after centrifugation and removal of contaminants. Using these volume values, we calculated the approximated outputs of each of the

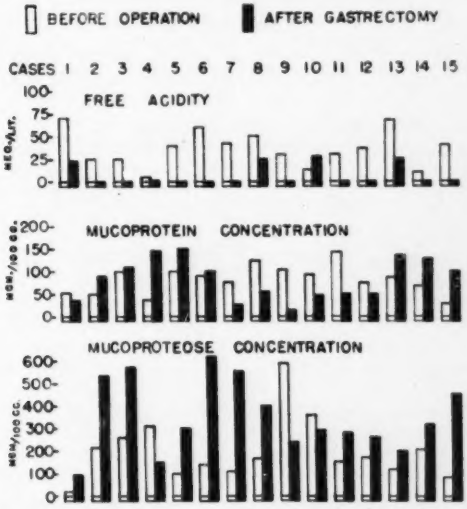


Fig. 1.—Average concentrations of free acid and gastric mucous substances during insulin tests in 15 patients with peptic ulcer before and after subtotal gastrectomy.

components. There is a known limitation due to escape of some part of the juice into the duodenum. These values are similar to those obtained by constant aspiration [14] and can be used for comparative purposes, since the conditions of each test are similar.

EFFECT OF SUBTOTAL GASTRIC RESECTION ON GASTRIC SECRETION

Partial resection was performed on 25 patients, 21 of whom had peptic ulcer. The technic used was a modified Hoffmeister resection, with closure of the upper half of the cut end of the stomach and the performance of an antecolic anastomosis between the cut end of the stomach and the side of the jejunum. The efferent loop was brought to the lesser curvature. In 17 of these cases data were obtained preoperatively as well as postoperatively.

14. Ihre, B.: Human Gastric Secretion: A Quantitative Study of Gastric Secretion in Normal and Pathological Conditions, Acta med. scandinav., 1938, supp. 95, p. 1.

Figure 1 summarizes data obtained during the insulin test before and after subtotal gastrectomy in 15 patients with peptic ulcer. Each value represents the mean concentration calculated from all five specimens collected during the test. The postoperative studies were done in 10 of these cases (nos. 2, 3, 4, 6, 8, 9, 10, 12, 13 and 14) between two and a half and four weeks after operation, in four cases (nos. 1, 5, 7 and 15) within the second month after operation and in one case (no. 11) two and a half months after operation.

In 11 (73 per cent) of these 15 cases studied, a complete absence of acid secretion was noted before and after insulin, and in three of the remaining four cases there was a decrease of acid secretion by about one half. The concentration of mucoprotein in the gastrectomized stomach, on the other hand, showed a decrease in concentration in seven of the 15 cases, while in eight cases it was increased. The concentration of the second mucous component, dissolved mucoproteose, showed a decrease in three of these 15 cases and a distinct increase in 12 cases.

Figure 2 shows the average curves of gastric secretion in response to insulin before and after resection. This figure includes data on eight additional cases, not

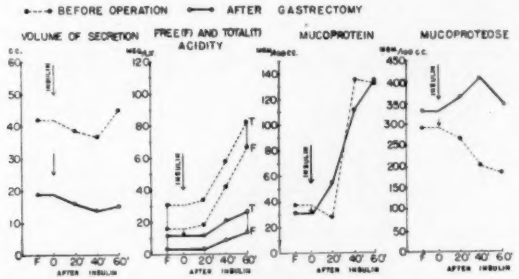


Fig. 2.—Average curves of gastric secretion during insulin test before (17 patients) and after (25 patients) subtotal gastrectomy.

studied preoperatively, in which gastrectomy was performed and in which postoperative studies were made at the end of three weeks in three cases and between one and three years in five cases. The changes observed in gastric secretion under fasting conditions and after insulin stimulation in gastrectomized patients consisted in a decrease in volume and acidity of gastric secretion, no change in concentration of dissolved mucoprotein and a definite increase in the concentration of the mucoproteose fraction.

The effects of gastrectomy on the total outputs of each of the gastric secretory products are shown in detail in figures 3 and 4. In 11 of 12 cases (92 per cent) of peptic ulcer, a decrease was observed in the volume of gastric juice and in the output of hydrochloric acid and gastric mucoprotein. The second mucous component, the gastric mucoproteose, showed changes in both directions—a decrease in seven and an increase in five of the 12 cases studied.

The statistical evaluation of the data observed in the period after subtotal gastrectomy for ulcer as compared with the preoperative period which are listed in table 1 indicates the following statistically significant changes: (1) a decrease

in the volume of gastric secretion (by 60 per cent); (2) a decrease in the concentration (by 88 per cent) and the output (by 95 per cent) of the free hydrochloric acid; (3) a decrease in the output of mucoprotein fraction of gastric mucin (by 65 per cent) at rather unchanged concentration in the gastric juice; (4) an increase

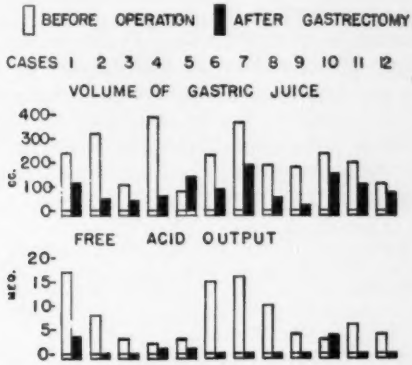


Fig. 3.—Output of gastric juice and acid during insulin test in 12 patients with peptic ulcer before and after subtotal gastrectomy.

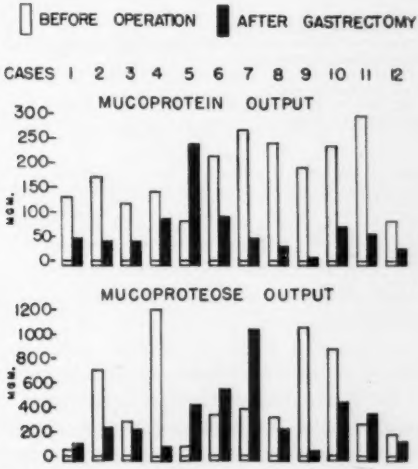


Fig. 4.—Output of gastric mucous substances during insulin test in 12 patients with peptic ulcer before and after subtotal gastrectomy.

in the concentration of gastric mucoproteose fraction (by 66 per cent) with unchanged total output.

Comment.—The decrease in the output of the acid secretion after gastrectomy is greater than the average drop in the total volume of gastric secretion. This is

due to the simultaneous decrease in concentration of acid which occurs in these circumstances. The latter may be only partly due to the increase in the amount of gastric buffers in the gastrectomized stomach because a similar drop is observed also in regard to total acidity (fig. 2). Rather it should be interpreted as the result of the removal of the antrum,[15] which is known to be the site of the specific humoral stimulant for acid secretion.

There is no decrease in the concentration of the gastric mucoprotein. The decrease in the output of mucoprotein parallels the decrease in total volume of gastric secretion. It may be due exclusively to the reduction of the surface area of the gastric mucosa secreting this glandular component. It is probable, therefore, that the preserved portion of the stomach, the upper part of the fundus, secretes the mucoprotein per unit of secreting surface at a rate approximately similar to the rate at which the resected corpus secretes it.

TABLE 1.—*Statistical Evaluation of Effect of Subtotal Gastric Resection in Twelve Patients with Peptic Ulcer on Secretion of Gastric Juice, Gastric Acid and Dissolved Gastric Mucoprotein and Mucoproteose, as Studied by Insulin Stimulation* *

	Means with Standard Error					
	Before Operation	After Operation	D †	ED †	t †	P at n = 11 †
Volume of gastric secretion, cc.	223 ± 27	91 ± 14	—132	30.4	4.44	0.001
Concentration of free acid, mEq./liter gastric juice	31 ± 6	4 ± 3	— 27	6.7	4.18	0.01—0.001
Output of free acid, mEq.	7.5 ± 1.4	0.5 ± 0.4	— 7	1.5	4.67	Less than 0.001
Concentration of mucoprotein dissolved in gastric juice, mg./100 cc. gastric juice	88 ± 9	74 ± 13	— 14	16.7	0.84	Not significant
Output of mucoprotein dissolved in gastric juice, mg.	179 ± 24	63 ± 17	—116	28.6	4.05	0.01—0.001
Concentration of mucoproteose dissolved in gastric juice, mg./100 cc. gastric juice	216 ± 44	360 ± 48	+154	75.3	2.21	0.05—0.02
Output of mucoproteose dissolved in gastric juice, mg.	479 ± 111	319 ± 70	—160	138.0	1.16	Not significant

* The data were collected in each case a few days before the operation and two to four weeks after operation. The volume of secretion is the sum of the fasting secretion (two specimens collected at intervals of 20 minutes) and of the three specimens collected within one hour after the intravenous injection of 16 units of regular insulin. The outputs of free acid, mucoprotein and mucoproteose were considered as the sum of the contents of respective components in two fasting specimens and three specimens collected within one hour after insulin. The concentrations of free acid, mucoprotein and mucoproteose represent the average values calculated as means from all collected samples.

† D = difference of means before and after operation, ED = standard error of the difference of the means, n = number of patients studied, minus one, t = D/ED, test of significance of difference of the means, and P = probability value of significance of difference of the means, calculated from table 3 in the Fisher-Yates statistical tables. Only differences showing values of P below 0.05 were accepted as statistically significant; those below 0.02 are highly significant.

The concentration of the second mucous substance, dissolved gastric mucoproteose, increases after gastrectomy in roughly similar proportion as the volume of gastric juice decreases. Since the mucoproteose is the product of dissolution and degradation of the visible surface epithelium mucus, its concentration in the gastric content must increase whenever the volume of gastric juice decreases and decrease whenever the volume of gastric juice increases. The first situation occurs in the gastrectomized patient. This inverse relationship between the volume and acidity of the gastric juice on one side and the concentration of the mucoproteose on the other also has been observed during daily examinations of a patient with a fistulous

15. Glass, G. B. J., and Wolf, S.: Hormonal Mechanisms in Nervous Mechanism of Gastric Acid Secretion in Humans, Proc. Soc. Exper. Biol. & Med. **73**:535, 1950.

stomach.[16] The high pH of the gastric contents in these circumstances, which favors the splitting of visible surface epithelium mucus and formation of the dissolved mucoproteose,[17] may also contribute to this phenomenon.

The total output of gastric mucoproteose after gastrectomy is only insignificantly changed in spite of the reduction in the secreting surface to one third or one fourth of the previous area. Consequently, it must be concluded that the formation of the substrate, i. e., surface epithelium mucus, is increased in the gastrectomized stomach per unit of secretory surface. This may corroborate the gastroscopic and histologic reports which indicate a high incidence of postgastrectomy gastritis.[18]

EFFECT OF BILATERAL VAGOTOMY ALONE AND IN ASSOCIATION WITH SUBTOTAL GASTRIC RESECTION ON GASTRIC SECRETION

Vagotomy Alone.—Five patients were studied by means of the insulin test at periods varying from five months to four years after bilateral vagotomy. In two of these cases the transthoracic and in three the transabdominal approach was used. In two cases gastroenterostomy and vagotomy were performed. The data are summarized in figure 5.

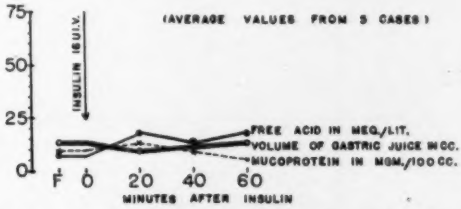


Fig. 5.—Gastric secretion after insulin stimulation in patients with peptic ulcer after bilateral vagotomy alone.

It is evident from this figure that the vagotomized stomach showed not only the depression of the acid secretion but also that of the gastric mucoprotein. Moreover, the normal response of the gastric mucoprotein to insulin, which is characterized by a sharp rise of mucoprotein concentration 40 to 60 minutes after intravenous administration of insulin, was abolished after complete bilateral vagotomy. In this respect, the behavior is similar to the acid response. However, we have also observed in two cases, studied one and a half and four years after simple vagotomy, that the response of acid to vagal stimulation with insulin was partly restored while the response of mucoprotein was still abolished.

The average concentration of the second mucous component, gastric mucoproteose, was found definitely increased under fasting conditions in the vagotomized

16. Wolf, S., and Glass, G. B. J.: Correlation of Conscious and Unconscious Conflicts with Changes in Gastric Function and Structure: Observations on the Relation of the Constituents of Gastric Juice to the Integrity of the Mucous Membrane, Life Stress and Bodily Disease, A. Res. Nerv. & Ment. Dis., Proc. **29**:665, 1950.

17. Glass, G. B. J.; Pugh, B. L.; Grace, W. J., and Wolf, S.: Observations on the Treatment of Human Gastric and Colonic Mucus with Lysozyme, J. Clin. Invest. **29**:12, 1950. Glass and Boyd.[10b]

18. Footnotes 6 *c*, *d*, *e*, *f* and *g*.

stomach, as compared to the normal stomach, the average in the former amounting to 368 mg. per 100 cc. of gastric juice.

Comment: The concentrations and outputs of the gastric mucous substances after vagotomy show a divergent pattern. The secretion of one of the mucous components, mucoprotein, is completely depressed, in the same way as is the secretion of hydrochloric acid and pepsin from the gastric glands.[12] On the contrary, the formation of the second mucous component, which is derived from the surface epithelium lining of the gastric mucosa, is increased. The latter finding indicates by inference that there is an increased secretion of the substrate from which this substance forms, i. e., of the visible surface epithelium mucus, which increase must be simultaneously associated with the increased dissolution and degradation of this mucous-coating layer. The conditions for the digestion of the surface epithelium mucus are favorable in the vagotomized stomach because of the high pH of the stomach content as well as the prolonged emptying time of the stomach. This increased degradation of the surface epithelium mucus may explain why in the

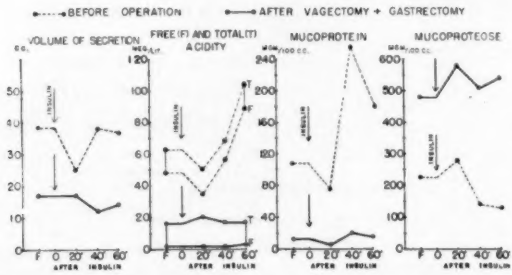


Fig. 6.—Average curves of gastric secretion in 5 patients with peptic ulcer before and after bilateral vagotomy associated with gastrectomy.

vagotomized stomach no evidence of increased mucus formation has been found on direct visual [5] or gastroscopic examination [6a, b] and why an increased mass of mucinous material dissolved in the gastric juice has been noted in the stomachs of these patients.[19]

Bilateral Vagotomy Associated with Subtotal Gastrectomy.—In five patients with peptic ulcer the combined operation of bilateral vagotomy and partial gastrectomy by means of a transabdominal approach was performed. All cases were studied by means of the insulin test a few days before operation and two and a half to four weeks thereafter. The data are graphically represented in figure 6, and summarized in table 2. The results obtained were similar to those observed after simple vagotomy. However, the depression of the acid secretion was greater in cases of combined operation than after simple vagotomy, which confirms previous inferences of other workers.[3d] The concentration and output of dissolved mucoproteose under these conditions were higher than after vagotomy alone. The depression of the mucoprotein secretion was of similar extent in both instances.

19. Bockus, H. L.: Discussion, in Bockus, H. L.: Postgraduate Gastroenterology, Philadelphia, W. B. Saunders Company, 1950, p. 70.

TABLE 2.—*Statistical Evaluation of the Effect of Bilateral Vagotomy Associated with Partial Gastric Resection in Five Patients with Peptic Ulcer on Secretion of Gastric Juice, Gastric Acid and Dissolved Gastric Mucoprotein and Mucoproteose, as Studied by Insulin Stimulation* *

	Means with Standard Error					
	Before Operation	After Operation	D	E_D	t	P at n = 4
Volume of gastric secretion, cc.	176 ± 63	79 ± 23	− 97	67	1.45	Not significant
Concentration of free acid, mEq./liter gastric juice	55 ± 11	0 ± 0	− 55	11	5.00	0.01—0.001
Output of free acid, mEq.	99 ± 29	0 ± 0	− 99	29	3.41	0.05—0.02
Concentration of dissolved mucoprotein, mg./100 cc. gastric juice	145 ± 47	14 ± 4	−131	45	2.97	0.05—0.02
Output of dissolved mucoprotein, mg.	263 ± 96	10 ± 1	−253	96	2.63	about 0.05
Concentration of dissolved mucoproteose, mg./100 cc. gastric juice	202 ± 52	520 ± 104	+318	116	2.74	0.05
Output of dissolved mucoproteose, mg.	366 ± 210	602 ± 224	+236	307	0.77	Not significant

* See footnotes to table 1.

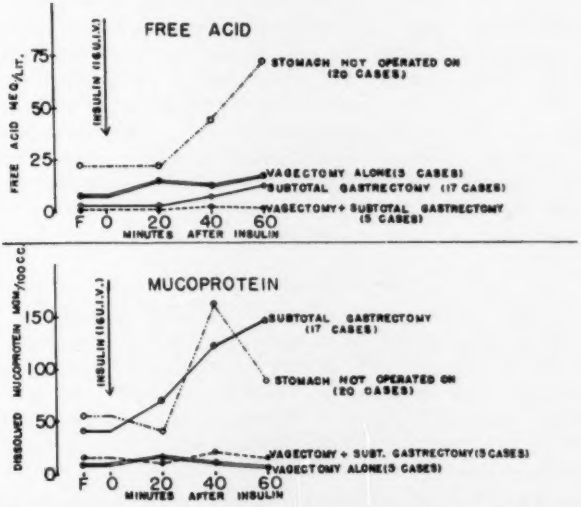


Fig. 7.—Average concentrations of acid and mucoprotein after insulin in stomachs with peptic ulcer on the basis of operation and nonoperation.

The following statistically significant average changes during the insulin test were found after vagotomy associated with subtotal gastric resection (table 2): (1) abolition of the hydrochloric acid secretion under fasting conditions and after insulin stimulation; (2) decrease in the concentration of the mucoprotein fraction in the gastric juice by 90 per cent and drop of its output to 4 per cent of initial values; (3) increase in the concentrations of the mucoproteose fraction in the gastric content by more than 150 per cent.

Comment: The testing of the mucoprotein response to insulin after vagotomy associated with gastric resection may provide the information which cannot be obtained by testing the gastric acidity response to insulin alone. The latter is abolished or is on a low level in both vagotomized and gastrectomized stomachs, so that the negative acid response to insulin in such instances may depend on

vagotomy as well as on gastric resection itself. In such cases the mucoprotein response to insulin may give a clue to the proper interpretation of the negative acidity response to this stimulation. The negative response of both acid and mucoprotein to insulin would indicate within known limitations [2] that the nervous pathways to the stomach were severed. On the other hand, the negative acid response and positive mucoprotein response to insulin in these circumstances would indicate that the negative result of the Hollander test was due mainly to gastrectomy and not to vagotomy, since the mucoprotein response to insulin was abolished after vagotomy but preserved in the gastrectomized stomach. This fact is best illustrated by graphs drawn in figure 7.

Another conclusion can be drawn from the findings concerning the secretion of mucous fractions in the vagotomized stomach. There is no evidence that the gastric mucosa in the vagotomized stomach is better protected against peptic digestion or trauma than that of the stomach not operated on or than that after gastrectomy alone. The slightly increased buffering effect of the increased content of mucoproteose in the gastric juice is counteracted by the simultaneous abolition of the secretion of gastric mucoprotein. It is of no importance to the protection of the gastric mucosa, since no or little hydrochloric acid is secreted by the nonvagotomized stomach. On the other hand, the increased degradation of the surface epithelium mucous coating of the vagotomized stomach, which is manifested by the increased concentration and unchanged output of gastric mucoproteose in the stomach, cannot contribute to the better protection of the gastric mucosa. Because of this feature the mucosa of the vagotomized stomach may be even more susceptible to trauma than when its mucous coating is fully preserved.

SUMMARY AND CONCLUSIONS

Two statistically significant changes were observed in the secretion of mucous substances in the human stomach after subtotal gastric resection, which were (1) an increase (on the average by 66 per cent) of the concentration of mucoproteose fraction of mucin, which represents the dissolution and degradation product of the mucous surface epithelium lining of the stomach, and (2) a decrease in the output (on the average by 65 per cent) of the glandular mucoprotein, which is the component of mucin secreted by mucous cells of gastric glands.

The first change indicates an increased rate of formation of surface epithelium mucus in the remaining part of the stomach after operation and may corroborate the observations concerning the high incidence of postgastrectomy gastritis in these patients. The second is due to operative removal of a great part of mucoprotein-secreting mucosal surface. Since this decrease in output of mucoprotein was similar in quantity to that of the total volume of gastric secretion after operation and since the concentration of the mucoprotein in the gastric juice of the subtotally resected stomach was practically unchanged as compared with that in the preoperative period (both under fasting conditions and after insulin stimulation), it is probable that the rate of formation of mucoprotein by glands of the upper part of the fundus is similar to that of the lower part of the fundus and the corpus of the stomach which underwent resection.

After successful bilateral vagotomy the secretion of gastric mucoprotein was completely depressed and the increase in its concentration, which occurs normally

after intravenous administration of insulin, was completely abolished in the same way as that of hydrochloric acid and pepsin. Since the response of mucoprotein to insulin is preserved after gastrectomy, it may differentiate the negative response of acid to insulin due to gastrectomy from the negative acid response due to vagotomy in cases in which the vagotomy was associated with subtotal gastric resection.

The concentration of the gastric mucoproteose (of surface epithelial origin) showed, on the contrary, a definite increase after vagotomy alone or combined with gastric resection. This indicates an increased formation and exaggerated degradation of the mucous surface epithelium lining in the vagotomized stomach, especially after combined operation. The degradation of the mucous coating of the stomach after vagotomy cannot be considered a favorable feature which might contribute to a better protection of the gastric mucosa from trauma or peptic digestion.

OBSERVATIONS ON THE MAJOR RADICLES OF THE EXTRAHEPATIC PORTAL SYSTEMS

HARRY K. PURCELL, M.D.
JOHN J. CONNOR, M.D.
WILLIAM F. ALEXANDER, Ph.D.
AND
NIALL M. SCULLY, M.D.
ST. LOUIS

IN REVIEWING the literature on the anatomy of the extrahepatic portal system in the light of present day surgical procedures for the relief of portal hypertension, we were able to find little information on the length and caliber of the major vessels making up the extrahepatic portal systems.[1] In the performance of anastomoses between the portal system and the systemic circulation, it is important that the vessels used should have sufficient caliber to be able to transport enough blood in a given time to relieve the hypertension in the portal system. Because there is so little known about the length of these veins in the average person and because there is virtually nothing recorded in the literature concerning the caliber of the veins that are available for these anastomoses, this study was undertaken.

Since the study was begun, Douglass, Baggenstoss and Hollinshead,[2] of the Mayo Clinic, have reported variations in the make-up of the extrahepatic portal system and measurements of the veins in 92 dissections.

METHOD OF PROCEDURE

Fresh autopsy material was used in an attempt to simulate the condition of the living person as closely as possible. The majority of specimens were obtained at the St. Louis City Morgue, and the remainder of the bodies were examined at St. Mary's Group of Hospitals. Cases in which intra-abdominal disease was present that might distort the normal anatomy were eliminated. Cases in which there had been profuse bleeding from any source were also discarded because of possible distortion of the veins due to acute loss of blood.

From the Department of Surgery and Anatomy, St. Louis University School of Medicine.

Presented before the Forum on Fundamental Surgical Problems, American College of Surgery, Boston, 1950.

1. Morris, H.: Morris' Human Anatomy: A Complete Systematic Treatise, ed. 10, Philadelphia, The Blakiston Company, 1942, p. 1635. Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 23, Philadelphia, Lea & Febiger, 1936, p. 1381.

2. Douglass, E.; Baggenstoss, A. H., and Hollinshead, W. H.: Variations in the Portal Systems of Veins, Proc. Staff Meet., Mayo Clin. **25**:26-31 (Jan. 18) 1950.

The circumference of a vein was measured by carefully isolating a portion of the vessel and lightly suspending it over a narrow metal strip so that the vessel was caused to be flattened. This measurement, which was taken across the flattened portion of the vessel, represented one half of the circumference. The circumference of the vessel was then computed by multiplying this figure by two, and from this circumference the diameter was computed in the ordinary way. The diameter of each of the vessels was measured at the point where the vessel would be divided if it were used for an end to side portacaval anastomosis. For example, the diameter of the portal vein was taken at the bifurcation of the portal vein, and the diameter of the superior mesenteric vein was taken at the most caudad portion of the main trunk of the vein.

The total length of each vessel was measured carefully in centimeters, and this measurement is called the "anatomical length." When only a part of a vessel was surgically accessible, the length of this surgically accessible portion was measured and is called the "surgical length."

TABLE 1.—*Dissections of Veins of the Portal System*

Number of cases	100
Average age	51.9
Number of males	83
Number of females	17

TABLE 2.—*Portal Vein*

Average length	
Surgical	4.02 cm.
Anatomical	7.34 cm.
Greatest surgical length	7.0 cm.
Smallest surgical length	2.0 cm.
Average diameter	1.09 cm.
Greatest diameter	1.59 cm.
Smallest diameter	0.47 cm.
59% of all diameters measured	1.09 cm. or more
Tributaries	
No branches	14%
Cystic	61%
Coronary	67%
Pyloric	14%
Caudate	5%

A portion of a vessel was considered surgically inaccessible when it was surrounded by or isolated from the surgical field by an anatomical structure which prevented the vessel from being mobilized for use in an anastomosis.

RESULTS

One hundred bodies were dissected (table 1). Eighty-three per cent of the bodies were those of males, and 17 per cent were those of females.

Portal Vein (table 2).—The average surgical length of the portal vein was 4.02 cm. and the average anatomical length 7.34 cm. The greatest surgical length was found to be 7.0 cm. and the smallest surgical length 2.0 cm. The average diameter of the portal vein was 1.09 cm. The greatest diameter was found to be 1.59 cm. and the smallest diameter 0.47 cm. The diameter of 59 per cent of all portal veins measured was 1.09 cm. or more. The data on tributaries of the portal vein were as follows: no tributaries, 14 per cent; cystic vein, 61 per cent; coronary vein, 67 per cent; pyloric vein, 14 per cent; a branch from the caudate lobe of the liver, 5 per cent.

Splenic Vein (table 3).—The average length of the splenic vein was 10.54 cm. and the average diameter 0.53 cm. for the proximal end and 0.43 cm. for the distal end. The greatest distal diameter found in all dissections measured 1.27 cm. and the smallest distal diameter 0.12 cm. The distal diameters of 56 per cent of all dissections of the splenic vein measured 0.43 cm. or more. The distribution of tributaries of the splenic vein was as follows: pancreatic branches, 100 per cent; inferior mesenteric vein, 44 per cent; coronary vein, 27 per cent.

Superior Mesenteric Vein (table 4).—The average surgical length of the superior mesenteric vein was 3.39 cm. and the average anatomical length 6.08 cm. The greatest surgical length found in all dissections was 15 cm. and the smallest

TABLE 3.—*Splenic Vein*

Average length	10.50 cm.
Proximal	0.53 cm.
Average diameter, distal	0.43 cm.
Greatest distal diameter	1.27 cm.
Smallest distal diameter	0.12 cm.
56% of all distal diameters measured more than	0.43 cm.
Tributaries	
Pancreatic	100%
Inferior mesenteric	44%
Coronary	27%

TABLE 4.—*Mesenteric Veins*

Superior Mesenteric Vein	
Average length	
Surgical	3.39 cm.
Anatomical	6.08 cm.
Greatest surgical length	15 cm.
Smallest surgical length	1.0 cm.
(Two veins had no significant surgical length)	
Average diameter	0.78 cm.
Greatest diameter	1.209 cm.
Smallest diameter	0.25 cm.
46% of all specimens had diameters of	0.78 cm. or more
27% of all specimens had diameters of	0.95 cm. or more
Inferior Mesenteric Vein	
Average length	5.97 cm.
Average diameter	0.24 cm.
Termination of inferior mesenteric vein	
Superior mesenteric	53%
Splenic vein	28%
Both	16%
At junction of superior mesenteric and splenic	3%

surgical length 1.0 cm. (Two veins have no significant surgical length.) The average diameter was 0.78 cm. The greatest diameter found was 1.209 cm., and the smallest diameter was 0.25 cm. Forty-six per cent of all specimens had diameters of 0.78 cm. or more. Twenty-seven per cent of all specimens had diameters of 0.95 cm. or more.

Inferior Mesenteric Vein (table 4).—The average length of the inferior mesenteric vein was 5.97 cm. and the average diameter 0.24 cm.

Termination of the Inferior Mesenteric Vein (table 4).—The inferior mesenteric vein emptied into the superior mesenteric vein in 53 per cent of the dissections; into the splenic vein in 28 per cent; into both superior mesenteric vein and splenic vein (two branches) in 16 per cent and into the junction of the superior mesenteric and splenic veins in 3 per cent.

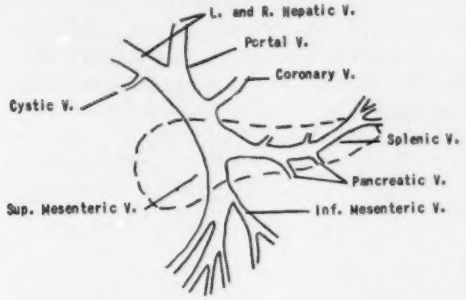


Figure 1.—Major veins of the extrahepatic portal system, type I. Inferior mesenteric vein entering the superior mesenteric vein, noted in 53 per cent of the cases. Coronary vein entering the portal vein, noted in 67 per cent.

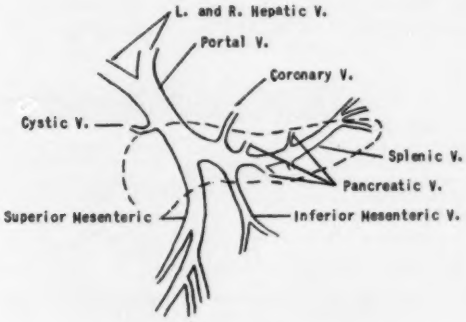


Figure 2.—Major veins of the extrahepatic portal system, type II. Inferior mesenteric vein entering the splenic vein, noted in 28 per cent of the cases. Coronary vein entering the splenic vein, noted in 27 per cent.

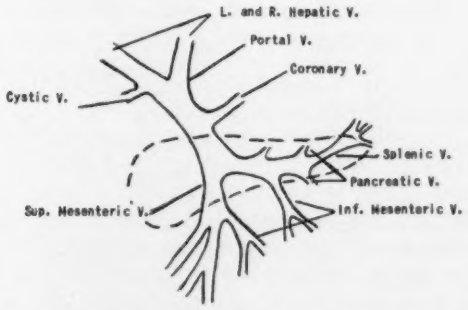


Figure 3.—Major veins of the extrahepatic portal system, type III. Inferior mesenteric veins entering both the superior mesenteric and the splenic vein, noted in 16 per cent of the cases. Coronary vein entering the portal vein, noted in 67 per cent.

Left Renal Vein (table 5).—The average length of the left renal vein was 8.31 cm. and the average diameter 0.92 cm.

The relation of the portal vein to the inferior vena cava is as follows: In 59 per cent of the cases the inferior vena cava passed posterior to the middle and distal thirds of the portal vein, in 32 per cent it passed posterior to the middle and proximal thirds of the portal vein and in 9 per cent it passed posterior to the proximal third of the portal vein. Obviously, the fact that the inferior vena cava in the majority of cases lies near to the distal end of the portal vein makes it easier to perform an end to side anastomosis between the portal vein and the inferior vena cava.

We have observed three major arrangements in the make-up of veins of the extrahepatic portal system (figs. 1, 2, 3).

Type 1. The inferior mesenteric vein empties into the superior mesenteric vein in 53 per cent of the cases, and the coronary vein enters the portal vein in 67 per cent of the cases (fig. 1).

Type 2. The inferior mesenteric vein enters the splenic vein in 28 per cent of the cases and the coronary enters the splenic vein in 27 per cent (fig. 2).

TABLE 5.—*Left Renal Vein*

Average length	8.31 cm.
Average diameter	0.92 cm.
Relation of Portal Vein to Inferior Vena Cava	
Inferior vena cava passes beneath middle and distal one third of portal vein	59%
Inferior vena cava passes beneath middle and proximal one third of portal vein	32%
Inferior vena cava passes beneath proximal one third of portal vein	9%

Type 3. The inferior mesenteric vein divides into two branches and enters both the superior mesenteric and the splenic vein, noted in 16 per cent of the cases (fig. 3).

COMMENT

We believe that these measurements taken from fresh autopsy material are somewhat applicable to living subjects. It is possible that there is some variation in the size of the vessels in the living and the dead or a variation in the postmortem change occurring in one vessel as compared to another. This could be influenced by various factors; such as the length of time allowed to elapse between death and the time of the dissection, the thickness of the vessel wall, the age of the patient or the presence of grossly undetected pathologic changes in the vessel wall. These factors must all be considered in the evaluation of this report, and we have attempted to cancel out some of these variations by averaging the results of 100 dissections. The anatomical arrangement of the extrahepatic portal system varies somewhat from the standard textbook description, as seen in the above figures. The inferior mesenteric vein empties into the superior mesenteric vein in 53 per cent of our dissections and into the splenic vein in only 28 per cent. The coronary vein enters the portal vein in 67 per cent of our cases and the splenic vein in only 27 per cent.

Figure 4 illustrates graphically the length and diameter of the major veins of the extrahepatic portal system and the left renal vein. It will be noted that among the veins of the extrahepatic portal system, the superior mesenteric has the next

largest diameter to the portal vein. The diameter of the superior mesenteric vein averages 0.78 cm.; therefore, it ranks second in caliber to the portal vein itself. The length of the surgically accessible portion of the superior mesenteric vein is 3.39 cm. The superior mesenteric vein is easily exposed by an incision through the posterior peritoneum just inferior to the root of the transverse mesocolon, as illustrated in figure 5. In view of its accessibility, these measurements and the close proximity of the superior mesenteric vein to the inferior vena cava (see fig. 6), it would seem reasonable to presume that the superior mesenteric vein should be a good candidate for use in the anastomosis between the portal and caval systems for the relief of portal hypertension.

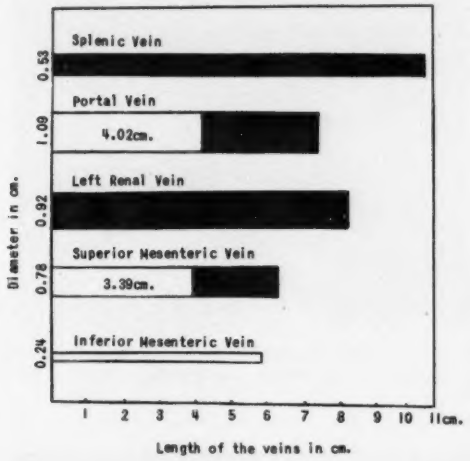


Figure 4.—Lengths and diameters of the major veins of the portal system and the left renal vein. Portion shown in black is the total length of the vein. Portion shown in white is the surgically accessible portion of the vein.

It is worthy of mention that in February of 1950 one of us (H. K. P.) performed an end to side anastomosis between the superior mesenteric vein and the inferior vena cava on a 3 year old boy who had suffered from 12 severe hemorrhages in one year, due to portal hypertension associated with a cavernomatous transformation of his portal vein and marked splenomegaly. The portal venous pressure before the operation was 520 mm. of saline solution. Portal venous pressure after anastomosis was 150 mm. of saline. Up to the present time the child has been symptom free. His splenomegaly has virtually disappeared, and he has shown no signs of hemorrhage from esophageal varices since the operation.

Because of the small diameter of the inferior mesenteric vein, we believe that we can justly conclude that the vein is far too small to be used effectively for the relief of portal hypertension.

Figure 5.—Photograph showing exposure of superior mesenteric vein. The transverse colon is reflected superiorly, and the vein is exposed through longitudinal incision at the base of the transverse mesocolon.

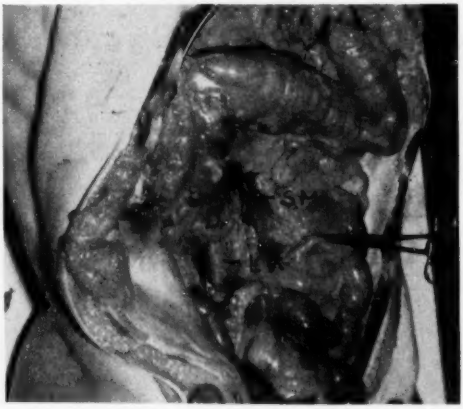


Figure 6.—Photograph of actual dissection showing the superior mesenteric vein and the inferior vena cava exposed.

CONCLUSIONS

1. The portal vein is relatively constant in length, caliber and its relation to surrounding structures; however, its tributaries are extremely variable.

2. The inferior mesenteric vein does not uniformly enter the splenic vein, as indicated in the standard textbooks, but oftener enter the superior mesenteric vein as demonstrated in this series of dissections.

3. The average diameter of the inferior mesenteric vein is 0.24 cm. We believe that this vessel is generally too small for effective use as an anastomotic channel between the portal and caval systems for the relief of portal hypertension.

4. The average diameter of the splenic vein is 0.43 cm., which is smaller than either the portal vein or the superior mesenteric vein.

5. Since the diameter of the superior messenteric vein averages 0.78 cm., it ranks second in caliber to the portal vein itself. The length of the surgically accessible portion of the superior mesenteric vein is 3.39 cm. We believe that the superior mesenteric vein is well suited for use in anastomosis between the portal and systemic venous systems for the relief of portal hypertension.

CORRECTION

In the article by Drs. Pack and Tabah on "Dermatofibrosarcoma Protuberans: A Report of Thirty-Nine Cases" in the March issue of the ARCHIVES, page 394, the fourth sentence under the side heading "*(b) Traumatic Origin*" should read "In McMaster's review of 39 cases collected from the literature and his own case, trauma was alleged to have preceded the initial appearance of the tumor in eight instances." The last complete sentence on this page should read "A 74 year old woman after an interval of 19 years discovered the tumor growing in the scar of an abdominal operation."

PAIN CONTROL FOLLOWING UPPER ABDOMINAL OPERATIONS

WALTER H. GERWIG Jr., M.D.
CHARLES W. THOMPSON, M.D.
AND
BRIAN BLADES, M.D.
WASHINGTON, D. C.

PULMONARY complications may follow any type of surgery. Pooler [1] has studied 5,869 surgical patients and found the occurrence of pulmonary morbidity following extra-abdominal, lower abdominal and upper abdominal operations to be 1 per cent, 11 per cent and 19 per cent, respectively. It is apparent, therefore, that every possible precaution should be employed to prevent these complications in patients who have undergone operations in the upper region of the abdomen. This is particularly true in poor risk patients, patients with pulmonary disease, the aged, and the emotionally unstable who are actual or potential narcotic addicts.

Pain diminishes respiratory excursions; there is a reluctance to cough or breathe deeply. Narcotics will relieve pain but will inhibit the important cough reflexes.

Pooler [1] has attempted to prevent pulmonary complications following operations by the use of intravenous injections of procaine hydrochloride. After administration of the drug he encouraged his patients to cough and carry out routine breathing exercises. It is questionable that a sufficient local concentration of procaine could be delivered by the intravenous route to relieve postoperative pain. Recently, Blades and Ford,[2] at the George Washington University, described a technic which appears to be valuable in reducing pain following operations on the chest. Their method consists of the implantation of polyethylene tubes in the incision in the chest wall prior to closure. Through these tubes, the ends of which are fixed in the dressing, procaine is injected. They indicated that their procedure, with slight modification, might be applied to surgery of the abdomen. Since the need for narcotics following chest operations was markedly reduced, it seemed reasonable that a modified technic for upper abdominal operations should be evaluated.

TECHNIC

Twenty-four patients undergoing cholecystectomy were studied in this series. The purpose was to establish the effectiveness of procaine injections through polyethylene tubes in upper abdominal wounds. One half of the cases were used as controls, while in the remainder three polyethylene tubes were placed beneath the anterior rectus sheath of the abdominal wound and

From the departments of surgery and medicine, the George Washington University School of Medicine.

1. Pooler, H. E.: Relief of Post-Operative Pain and Its Influence on Vital Capacity, Brit. M. J. **2**:1200-1203, 1949.

2. Blades, B., and Ford, W. B.: A Method for Control of Postoperative Pain, Surg., Gynec. & Obst. **91**:524-526, 1950.

the ends brought out through a lateral stab wound. These were placed so that procaine was delivered to the upper, middle and lower parts of the wound. The tubes were attached to no. 19 gage needles which had been pushed through a cork (fig. 1). Three cubic centimeters of 2 per

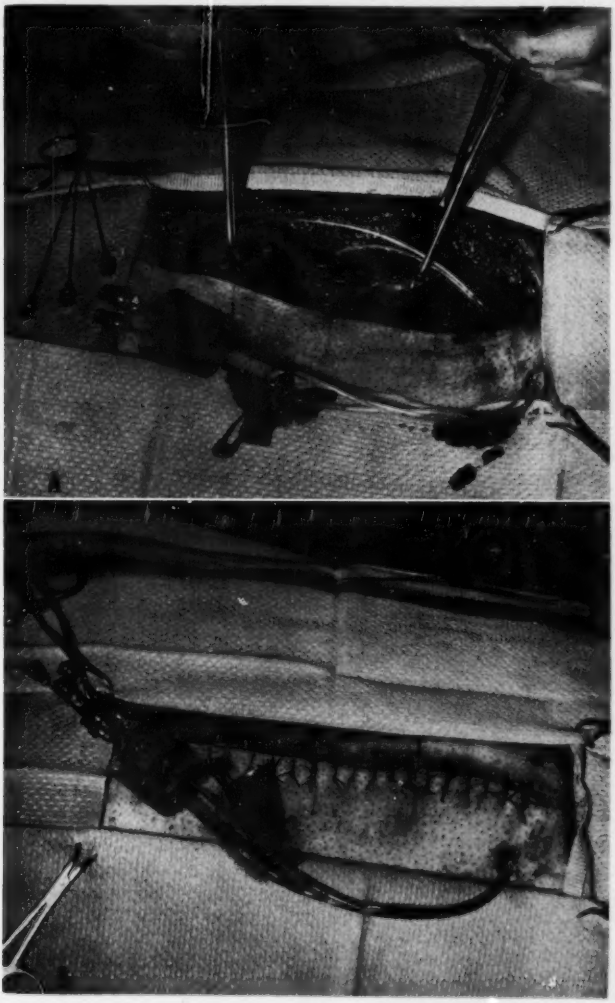


Fig. 1.—*A*, photograph of operative incision showing staggered position of polyethylene tubes prior to closure of the anterior rectus sheath. *B*, photograph of closed incision.

cent procaine solution was injected into each tube at three hour intervals. A comparative study of consumption of narcotics is recorded in tables 1 and 2. One particularly important case is reported in detail.

RESULTS

In both groups the need for reducing pain was greatest between the twelfth and thirty-sixth postoperative hours. In neither group was pain suppression necessary after the eighty-fourth hour. In the control group, an average of 11.1 hypodermic injections was necessary during the 60 hour period, while in the treated group the

TABLE 1.—*Narcotic Needs of 12 Patients During the First Sixty Hours Following Upper Abdominal Operation (Cholecystectomy)* *

Patient	Age, Yr.	Race	Sex	0-12 Hr.	13-36 Hr.	37-60 Hr.	61-84 Hr.	Total
E. C.	37	W	F	XX	XXXX	XXX	...	9
C. C.	38	W	F	XX	XXXXX	XXXXX	00	12
C. W.	63	W	F	XXXX	XXXX	XXX	0	11
S. L.	40	W	F	XXX	XX	XX	00	7
F. S.	28	W	F	XX	XXXXXX	XXXXXX	00000	14
D. T.	23	W	F	XXX	XXXXX	XX	...	10
E. S.	29	W	F	XX	XXXX	XX	...	8
R. H.	36	W	F	XXXXX	XXXXXX	XXXX	000	15
R. D.	32	W	F	XXX	XXXXXX	XXXXX	000	14
D. S.	56	W	M	XXX	XXXXXX	XXXX	00	13
M. K.	69	W	F	XXX	XXXXX	XXXXX	00	13
N. B.	53	W	F	XX	XXXX	XX	0	8
Totals:				34	57	43	...	134

Average: 11.1 narcotic injections per patient.

* X indicates hypodermic narcotic injection during first 60 hours; 0 indicates hypodermic narcotic injection after first 60 hours.

TABLE 2.—*Narcotic Needs of Twelve Patients When Procaine Was Periodically Injected Into the Wound Through Polyethylene Tubes* *

Patient	Age, Yr.	Race	Sex	0-12 Hr.	13-36 Hr.	37-60 Hr.	61-84 Hr.	Total
A. W.	53	W	F†	..	..	..	..	0
H. C.	32	W	F	..	X	..	..	1
W. L. S.	51	N	M	X	XX	XX	0	5
M. D.	57	W	F	..	XX	X	..	3
G. N. S.	62	W	M	X	XXX	X	0	5
E. B.	38	W	F	X	XX	X	0	4
P. F.	58	W	M	..	..	..	..	0
W. S.	47	W	M	XX	X	X	..	4
T. F.	42	N	M	X	XX	X	000 (codeine)	4
E. O'C.	43	W	M	X	XXX	X	00 (codeine)	5
R. B.	28	N	F	X	XX	XX	0	5
I. Y.	49	Chinese	M	..	X	..	..	1
Totals:				8	19	10	..	37

Average: 3 narcotic injections per patient.

* X indicates hypodermic narcotic injection during first 60 hours; 0 indicates hypodermic narcotic injection after first 60 hours.

† This is the patient reported on in detail.

average was three injections. There was also a greater need for narcotics in the control group between the sixtieth and eighty-fourth hours. The effect of this technic on the wound cannot be established from this small group of patients, but in our cases there was no interference of tissue repair. Follow-up studies revealed healing in the treated group to be complete in all instances.

It appears that adequate control of pain during the first 60 hours is most important. The tubes may be removed at this time. On the basis of the time of

removal of the tube it was felt that wound healing, fascia, muscle, fat and skin would not be materially influenced.

REPORT OF A CASE

The case of a desperately ill cripple with pulmonary disease is recorded in which the relief of pain without narcotics might well have been the lifesaving factor.

The patient, a 55 year old woman, had had symptoms of gallbladder disease for five years. By avoiding fatty foods she had been relatively free of symptoms. On her admission, the physical examination revealed exquisite tenderness in the right upper quadrant of the abdomen, fever, leukocytosis and other classical features of cholecystitis.

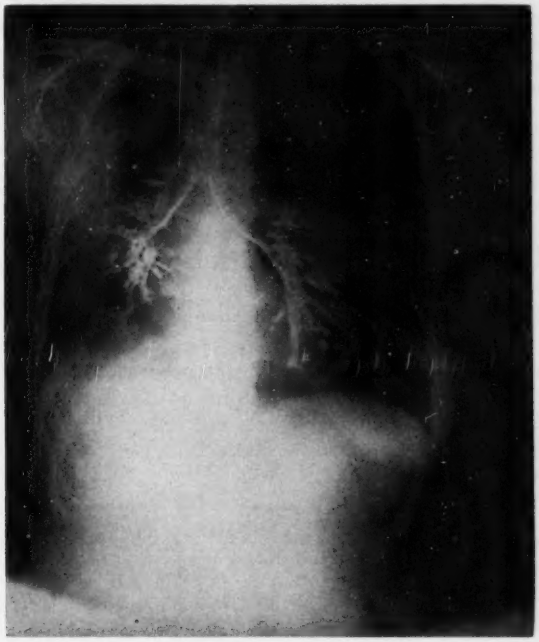


Fig. 2.—A bronchogram demonstrating extensive bronchiectasis and pulmonary fibrosis resulting from roentgen ray treatment.

Past History.—At the age of 12, after pertussis, a chronic cough developed which persisted for several months. Except for frequent "colds" she was relatively well until the age of 22, when she became desperately ill with influenza. Convalescence was prolonged, and after the influenza she was never free of a productive cough.

The diagnosis of bronchiectasis was established by bronchography in 1941. The patient continued to work, however, but had frequent colds, chest pain, occasional hemoptysis and bouts of fever. In 1944 bronchial pneumonia required hospitalization. In 1946 a simple mastectomy was performed for carcinoma of the breast. Nine months later an egg-sized lymph node in the right axilla was removed. Roentgen therapy was employed after this operation.

She was first seen by one of us (C. W. T.) in 1947 because of bronchiectasis and pulmonary fibrosis (fig. 2). Despite the fact that the original treatment had been employed for carcinoma of the breast, no sign of recurrence was detectable.

She had been able to work but had required treatment with antibiotics for three or four days at six week intervals because of fever, chest pain, purulent sputum and hemoptysis. The absolute necessity of surgical intervention for cholecystitis occurred when the patient was at a low level of efficiency and chronically ill and had been maintained on antibiotics and soluble sulfonamides for the preceding four or five days.

Since her progress indicated that surgical intervention for gallbladder disease was imperative, the pulmonary lesions could no longer be a detaining factor.

Operation.—Exposure of the gallbladder revealed a large, tense edematous organ filled with pus and stones. Despite the hazards of the moment, the postoperative course of this patient with chronic pulmonary disease was the factor of major importance. The choice of cholecystectomy versus cholecystostomy presented itself. Removal of the gallbladder offered only one postoperative seige; therefore, this procedure was chosen. Polyethylene tubes were inserted.

Postoperative Course.—Three cubic centimeters of 2 per cent procaine solution was injected at the three hour intervals. No narcotics were required for pain, and the cough reflex was not inhibited. Postural drainage was begun, producing the usual one-half to one cup of sputum each day, and the patient was ambulatory 10 hours after the operation. There were no postoperative complications. The wound healed firmly, and examination seven months later revealed a well healed incision.

COMMENT

Control of pain without suppression of respiratory excursions and the cough reflex is especially important after operation in the upper area of the abdomen. A control study has been carried out which indicates that the injection of procaine into the wound will reduce the need for narcotics during the first 60 hours following operation.

Since most postoperative pulmonary complications occur in the first three postoperative days it is apparent that the technic which has been described will be of value. This is particularly true for patients with pulmonary disease.

Intravenous administration of procaine hydrochloride cannot safely supply the local concentration of the drug necessary for pain relief. The procedure which we have described will guarantee a simple method for local analgesia in operative wounds.

It is important to emphasize that in no case in this series was the nurse instructed to employ procaine injections in lieu of a hypodermic injection or a narcotic.

It appears that if pain is controlled during the first 60 hours, the necessity for subsequent medication is reduced.

SIGNIFICANCE OF POSTOPERATIVE GLYCOSURIA AND KETONURIA IN NONDIABETIC ADULTS

ROBERT ELMAN, M.D.
AND
T. E. WEICHSELBAUM, Ph.D.
With the Technical Assistance of Marjorie A. Graul, R.N.
ST. LOUIS

EVEN though glycosuria and acetonuria are fairly common after operation, their exact significance is not generally known. Do they mean a serious disturbance in carbohydrate metabolism? Is the excretion of ketone bodies evidence of a transient overproduction thereof by the liver or of diminished utilization by peripheral tissue? Is the glycosuria the result of a diminution of peripheral utilization of glucose or of increased glycogenolysis? A number of surgical patients were observed in whom quantitative determinations of the 24 hour output of glucose and of acetone were made in an attempt to answer these questions. A few of these observations were briefly reported in a previous paper from this laboratory.[1]

PREVIOUS WORK

In an exhaustive report published in 1933, Roscher[2] studied and reviewed postoperative acidosis and ketonuria. A disturbance in acid-base balance was common, particularly in patients operated on under general anesthesia. A fall in the pH and in the carbon dioxide-combining power of the blood was observed. The changes, however, were slight in degree and short in duration. For example, the greatest drop in the pH was from 7.43 to 7.35 following a two hour gastric resection for duodenal ulcer in a 36 year old man under ether anesthesia. The pH returned to normal by the next day. The greatest fall in the carbon dioxide-combining power was after a thyroidectomy in a 49 year old woman under local anesthesia, who showed a drop from 60 to 39 volumes per cent in 24 hours, with no change in the pH. The value returned to normal by the second day. In most cases the values were completely normal six hours after operation, but in some they were not normal until 24, and occasionally 48, hours after operation.

Accompanying the change in the acid-base balance of the blood was a transient hyperglycemia, which was slight, reaching at most 204 mg. per 100 cc. It tended

Aided by a grant from the Commonwealth Fund.

From the Washington University School of Medicine, Department of Surgery, and Barnes Hospital.

1. Elman, R.; Lemmer, R. R.; Weichselbaum, T. E.; Owen, J. G., and Yore, R.: Minimum Postoperative Maintenance Requirements for Parenteral Water, Sodium, Potassium, Chloride and Glucose, Ann. Surg. **130**:703, 1949.

2. Roscher, F.: Postoperative Acidosis and Ketonuria, Acta chir. scandinav. (supp. 29) **74**:1, 1933.

to be even less in patients operated on under local or spinal anesthesia. It should be stressed that these patients received no dextrose orally or intravenously.

Extensive studies of the urine excreted after operation were also made by Roscher. Although ketone bodies appeared during the first 24 hours, ketonuria tended to be most marked during the second day after operation (at least in those who were not fed) and then gradually disappeared. The most marked degree of ketonuria was found in children, who also showed the most pronounced hyperglycemia. Ketonuria tended to be less frequent after local and spinal anesthesia and, moreover, frequently did not appear until the second postoperative day. Quantitative measurements of the urinary ketone bodies were carried out in all cases, using the gravimetric method of Van Slyke.[3] The highest value for the 24 hour output in adult patients was 650 mg. This was observed on the third postoperative day in a 16 year old youth following an appendectomy for acute appendicitis. A 36 year old man undergoing a gastric resection showed a maximum output of 520 mg. on the fifth postoperative day. By contrast, a 5 year old boy, after a two and a half minute tonsillectomy under ether anesthesia, showed a high output of 3.8 Gm. on the second postoperative day, illustrating the greater tendency for children to excrete ketone bodies than for adults.

That the ketonuria was probably due to starvation was indicated by a control observation made in a young adult who was given the same dietary intake as the postoperative patients but in whom no anesthesia or operation was carried out. In this case the maximum output of ketone bodies was 5.2 Gm. per 24 hours. Deuel and Gulick,[4] in a study of seven day fasts in man, found in one case on the third day a maximum loss of ketone bodies of 12.9 Gm. per square millimeter of body surface, although the average was half or less. The lessened ketonuria after operation as compared with simple starvation may be indicative of an inhibition of adipose tissue breakdown due to trauma. That protein tissue is more likely to furnish calories after operation is also indicated by the other observations of Roscher that the control case differed from the surgical cases in that there was no increase in nitrogen output in the urine so characteristic of the operative patient. It should be emphasized that Roscher's patients received merely 1 or 2 liters of Ringer's solution and at the most 500 cc. of 5 per cent glucose parenterally or by rectum each day during their postoperative periods. Thus nearly all patients suffered almost complete caloric and protein starvation for several days or until they took food by mouth. That little or no intravenous injections of dextrose were used probably accounted for the fact that in no patient was glycosuria found during any of the postoperative days.

These studies of Roscher confirmed the observations by Heidecker,[5] who also found postoperative ketonuria lasting 48 hours and sometimes up to five days. He noted that ketonuria was much more frequent in women (64 per cent) and children (63 per cent) as compared with men (36 per cent). Similar, too, was the finding that 65 per cent of patients under general anesthesia showed ketonuria, whereas

3. Van Slyke, D. D.: The Determination of B-Hydroxybutyric Acid, Acetoacetic Acid and Acetone in Urine, J. Biol. Chem. **32**:455, 1917.

4. Deuel, H. J., Jr., and Gulick, M.: Sexual Variation in Starvation Ketosis, J. Biol. Chem. **96**:25, 1932.

5. Heidecker, H.: Zur Frage der postoperative Acidose, Beitr. klin. Chir. **145**:709, 1929.

only 40 per cent exhibited this condition after local anesthesia, presumably because of the earlier resumption of food intake by mouth in the latter group. The amount of ketone bodies observed did not exceed 1.5 Gm. per 24 hours. Levy [6] had previously found that postoperative ketonuria was much more frequent in women than in men. Emerson,[7] in a study of rats, observed a far greater tendency for ketonuria after ether anesthesia in females than in males.

The same sex variation in ketonuria has also been observed by Deuel and Gulick [4] in human beings undergoing experimental starvation. The average excretion of ketone bodies in the urine per square meter of body surface on the fourth day was 2.66 Gm. in males and 6.5 Gm. in females. Moreover, the males showed little change in carbon dioxide-combining power, whereas the females showed a definite fall on repeated tests. Individual variations were rather slight except that some subjects, who were starved a second time after they had gained considerable body weight because of the deposition of fat, showed increased ketonuria.

Pareira and Somogyi [8] observed acetonuria in a postoperative patient during the infusion of 5 per cent dextrose, which disappeared when 10 per cent dextrose was given. They recommended the injection of 200 or 300 Gm. of dextrose well spaced throughout 24 hours in order to eliminate acetonuria. They assumed but did not prove that such an objective was important even in the nondiabetic patient.

The amount of dextrose required to prevent acetonuria after operation was studied in some detail in 68 surgical patients by Wren and Sachar.[9] The intake consisted of varying amounts of 5 or 10 per cent dextrose in water. The over-all incidence of acetonuria was rather high, considerably higher than that found in the present study. A positive reaction was obtained in 101 of 226 specimens examined, or 44 per cent. A lower incidence was noted in the first postoperative day (30 per cent) as compared with the second, third and fourth days (50 per cent). When 100 Gm. of dextrose were given, all specimens contained acetone bodies. Even when 300 Gm. were given, 24 per cent showed positive reactions. Of interest was the observation that 150 Gm. given to 14 patients in one continuous injection produced the same incidence (54 per cent) as that given 17 patients spaced throughout the 24 hours (55 per cent). In 13 patients given 200 Gm. of dextrose after spinal anesthesia, 25 per cent of the specimens showed acetonuria, whereas eight patients given 200 Gm. after ether anesthesia showed a higher incidence (64 per cent), which occurred on each of the four postoperative days.

The influence of the adrenal glands in ketosis was suggested by Mackay and Barnes,[10] who in female rats found that the ketonuria of fasting could be reduced

6. Levy, W.: Über postoperative Azetonurie, Deutsche med. Wchnschr., 1927, p. 916.

7. Emerson, G. A.: Sex Variation in the Ketonuria of Ether Anesthesia in Rats, J. Pharmacol. & Exper. Therap. **55**:90, 1935.

8. Pareira, M. D., and Somogyi, M.: Rationale of Parenteral Glucose Feeding in the Postoperative State, Ann. Surg. **127**:417, 1948.

9. Wren, C., and Sachar, L.: Amount of Carbohydrate Required to Prevent Ketonuria in Patients After Operation, Surg., Gynec. & Obst. **90**:349, 1950.

10. Mackay, E. M., and Barnes, R. H.: Influence of Adrenalectomy on Ketosis, Am. J. Physiol. **118**:184, 1937.

or eliminated by adrenalectomy. The difference by the third day was a reduction to one fourth and by the fourth day to one tenth of the control value. They also found that the ketonuria due to the injection of a ketogenic extract of the anterior pituitary was also reduced or eliminated by adrenalectomy. On the other hand, Shipley and Fry [11] found that the injection of various purified adrenal compounds had no influence on ketosis. However, they used male rats, which may have been of some significance.

The effect of trauma without anesthesia has been extensively studied by observing the accidentally injured, particularly those with fractures. A review and study by Sachar and others [12] showed that many patients suffer a transient impairment of glucose tolerance, presumably due to so-called traumatic diabetes.

Glycosuria as a postoperative finding, as already mentioned, was rare before the intravenous use of dextrose, a method of therapy which became extensive only in the past two decades. The report of Fantus [13] in 1936 was one of the first to point out the freqency of glycosuria after operation in patients receiving dextrose intravenously. He found that one third of the patients receiving between 150 and 200 Gm. of dextrose per day showed glycosuria, whereas the use of over 200 Gm. was followed by glycosuria in half of the cases. No quantitative data were presented, nor was there any report on the incidence or duration of diuresis. The classic paper by Woodyatt and others [14] on the relation between intravenous administration of dextrose and glycosuria appeared in 1915 and will be referred to later. It seems clear, however, that glycosuria following operation is not due to the effect of the operation itself except as it influences the rate of assimilation of intravenously injected dextrose.

The action of glycosuria in producing diuresis is an old observation. As long ago as 1899, Starling [15] observed the diuretic effects of glucose given in large amounts. A more recent study of glycosuria diuresis by Brodsky, Rapoport and West [16] showed that the phenomenon is the same in the normal person as in the diabetic patient. The mechanism depends only on the total number of osmotically active particles being excreted and is nonspecific, being shared by urea, salt, etc., as well as by glucose. These workers also studied the salt excretion during glucose diuresis and found a sharp increase in the loss of sodium and chloride in almost direct proportion to the rate of urine flow. By contrast, the loss of potassium and of phosphorus increased to only a slight extent.

Other studies have dealt with postoperative disturbances in carbohydrate metabolism, though not primarily with ketonuria or glycosuria. For example,

11. Shipley, P. A., and Fry, E. G.: Effect of Adrenal Cortical Compounds on Ketosis, Am. J. Physiol. **135**:460, 1942.

12. Sachar, L.; Walker, W., and Whittico, J.: Carbohydrate Tolerance, Blood Ketone Levels and Nitrogen Balance After Human Trauma (Fractures), Arch. Surg. **60**:837 (May) 1950.

13. Fantus, B.: Fluid Postoperatively (Especially Dextrose and Sodium Chloride): Statistical Study, J. A. M. A. **107**:14 (July 4) 1936.

14. Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injection of Sugar, J. A. M. A. **65**:2067, 1915.

15. Starling, E. H.: Glomerular Function of the Kidney, J. Physiol. **24**:317, 1899.

16. Brodsky, W. A.; Rapoport, S., and West, C. D.: The Mechanism of Glycosuria Diuresis in Diabetic Man, J. Clin. Invest. **29**:1021, 1950.

Koster[17] studied changes in the respiratory quotient following an intravenous infusion of dextrose before operation and at various periods after it. He found no differences and assumed that there was no disturbance in carbohydrate metabolism. However, the value of this method of procedure is questioned by Soskin and Levine.[18] A similar criticism may be made of studies of the lactic acid content of the blood by Castronuovo,[19] who injected 50 Gm. of dextrose intravenously as 330 cc. of a 15 per cent solution in 20 minutes several days before and about 15 hours after operation. No differences were observed in the blood lactic acid level. Moreover, there was little difference in sugar tolerance, for the degree of hyperglycemia following infusion was only slightly greater during the postoperative test. This study confirms the older observations that only a slight and transient disturbance in the blood glucose level occurs during and immediately after operation. Had Castronuovo repeated the sugar tolerance test two or three days after operation, more pronounced differences might have been found.

PRESENT STUDY

Observations were made on 394 twenty-four hour urine specimens obtained from 78 patients undergoing a variety of surgical procedures, all carried out with the patient under general anesthesia. No patient had any evidence of diabetes. In all cases, anesthesia consisted of induction with intravenously administered thiopental sodium (pentothal®) followed by nitrous oxide, oxygen and ether, frequently supplemented with curare. All the operations were intra-abdominal and varied from simple appendectomy to gastric, colic and abdominoperineal resections. The postoperative course was uneventful, and there were no deaths. Fifteen of the patients were observed for a period of two to five days before operation as well as for three to five days after operation. In all other cases, only the postoperative period was studied.

Patients were observed in a surgical metabolism ward where the 24 hour collections of urine could be assured. Each 24 hour specimen was collected under xylol for preservation, measured and an aliquot preserved in the refrigerator for analysis. Quantitative analysis of the urine for sugar was carried out by the Somogyi method.[20] Acetone was measured in terms of 1, 2, 3 or 4 plus, by means of the Legal (Rothera) nitroprusside test. It should be emphasized that a 4 plus reaction merely indicates that at least 100 to 200 mg. of acetone is being excreted per liter of urine but gives no information as to how much more of acetone or whether any acetoacetic acid or beta-hydroxybutyric acid is being excreted. Thus the test would be the same even if 20 to 30 Gm. of total ketone bodies were present in the same volume. For this reason, in seven specimens in which a 4 plus reaction was found quantitative measurements of the ketone bodies were carried out by means of the Van Slyke quantitative gravimetric procedure.[3]

17. Koster, H., and others: Intravenous Injection of Glucose: Its Effect on Respiratory Quotient, Am. J. Surg. **8**:970, 1930.

18. Soskin, S., and Levine, R.: Carbohydrate Metabolism: Correlation of Physiological, Biochemical and Clinical Aspects, Chicago, University of Chicago Press, 1946.

19. Castronuovo, J. J.: Utilization of Carbohydrate in Surgical Patients, Arch. Surg. **60**:845, 1950.

20. Somogyi, M.: A Rapid Method for the Estimation of Urine Sugar, J. Lab. & Clin. Med. **26**:1220, 1941.

All intake was intravenous, consisting of 2 liters per day. In 51 patients the daily intake was limited to 2 liters of 10 per cent dextrose in water or in half isotonic sodium chloride or of 5 per cent dextrose in water. Ten patients received 2 liters of 10 per cent dextrose plus a salt mixture. In 13 patients the solution contained 5 per cent dextrose and 5 per cent amigen® or Merck amino acids. In 4 cases 10 per cent dextrose solution containing 5 per cent each of amino acids and alcohol was given. In several cases the urine was collected in two successive 12 hour periods of each day. In all cases the intravenous injections of fluids were given during the first 12 hours, usually 1 liter in the morning and 1 liter in the afternoon. The average duration of the injection was between two and four hours, although considerable variation occurred. However, the period of injection was recorded in most cases, and the rate of infusion calculated therefrom.

FINDINGS

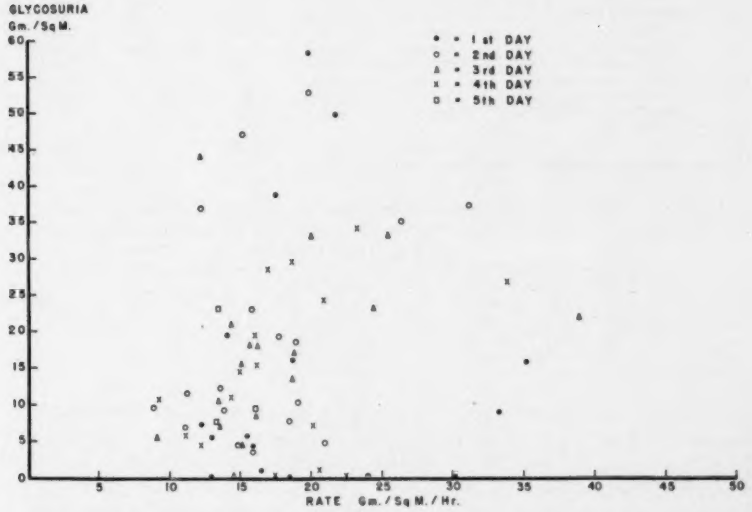
The observations made in the present study may be summarized under the three following headings: glycosuria, diuresis and acetonuria.

Glycosuria.—Of the 368 twenty-four hour urine specimens examined for their quantitative glucose content, 288, or 78 per cent, showed glycosuria, the incidence being the same for males and females. The incidence was lowest in those given only 2 liters of 5 per cent dextrose per day, for of 49 specimens only 23, or 48 per cent, contained sugar. Of the 78 patients studied, only 2 showed no glycosuria at any time; one was a male and one a female.

A comparison was made between the amount of glucose in the urine, and both the rate of injection and the postoperative day in a group of patients receiving 2 liters of 10 per cent dextrose each day. The findings are shown in the accompanying chart. While there is a general trend toward an increased glycosuria with increased speed of injection, there are so many exceptions that it seems clear that other factors play an important part. These factors are not apparent in the present study and would require more careful scrutiny of each case, particularly in regard to the influence of pain, drugs used for sedation, psychic factors and other elements. Similar wide variations were found in comparing the degree of glycosuria on the various postoperative days. Thus, careful examination of the chart shows a tendency toward a greater loss of glucose on the second and third days, which is also suggested by the data in tables 1 and 2. However, the correlation is not striking. On the other hand, glycosuria was no greater on the first day than on subsequent postoperative days. This would seem to show that the anesthesia and operation had little immediate effect. However, the oliguria which so often occurs on the day of operation in itself may have had some influence.

The amount of glucose actually lost is summarized in a group of patients listed in table 1. From these data wide variations are also apparent. However, more glucose was lost with the 10 per cent as compared with the 5 per cent solution. This can readily be explained by the fact that the injection in all cases was given over approximately the same interval—1 liter during two to four hours. Thus the rate of glucose administration with the 10 per cent solution was twice that with the 5 per cent solution. With this average period of injection, the daily loss of glucose with the 5 per cent solution was slight, averaging about 6 Gm. per day. However, as much as 24 to 31 Gm. out of the 100 Gm. injected was lost in a few

instances. By contrast, the average daily loss with the 10 per cent solution was much larger, i. e., between 21 and 36 Gm. Moreover, the maximum loss was 99 Gm., which is nearly 50 per cent of the 200 Gm. injected in this group. In patients given 100 Gm. (5 per cent) each of dextrose and amino acids per day (group 4), the loss of glucose was no greater than in groups 2 and 3 receiving 10 per cent dextrose alone. However, the loss in the third and fourth days was much less and indeed approached the minimum losses in group 1 (given 5 per cent dextrose), averaging only 9 Gm. of glucose per day. This was true despite the consistently greater incidence of acetonuria in these cases (see below). On the other hand, the four patients given 10 per cent dextrose in 5 per cent alcohol and 5 per cent amino acids (group 5) lost no more glucose than those receiving 10 per cent dextrose alone.



The relation between glycosuria and rate of glucose infusion. Each of the above points represents a 24 hour specimen. Note that while there is generally an increase in glycosuria with an increase in the rate of infusion, there are many exceptions indicating the influence of other factors. Note, moreover, that of the nine specimens showing little or no glycosuria, only one each were on the second and third postoperative days. There is a suggestion also that the degree of glycosuria tended to be greater on these two days. This correlation, however, is more definitely shown in tables 1 and 2.

In table 2 are the findings in 15 patients on whom data for at least two preoperative days were obtained for comparison with the postoperative period. In general, and despite marked variations in the rate of infusion and in other factors, it seems apparent that the loss of glucose was greater during the postoperative period as compared with the preoperative period. For example, of the 47 preoperative specimens, only 75 per cent contained glucose and the average daily loss was 12 Gm., as compared with the 66 postoperative specimens, of which 97

per cent contained glucose, the average daily loss being 23 Gm. There is some evidence that the postoperative loss was greatest on the second and third days, particularly in a few patients in whom the rate of infusion was kept at the same level throughout. For example, one patient (case 5, table 2) was given 2 liters of 10 per cent dextrose each during exactly three hours for two days before cholecystectomy and four days after. The amount of glucose excreted on each of the successive 24 hour periods was 10, 5, 7, 20, 32 and 14 Gm. No specimens con-

TABLE 1.—*Degree of Glycosuria (Grams/Twenty-Four Hours)*

			Postoperative Days *			
Group			1	2	3	4
1	5% dextrose in water, 2 liters/day	Average	8 (9)	6 (11)	7 (11)	3 (7)
		Range	0-16	0-31	0-24	0-14
2	10% dextrose in half isotonic saline, 2 liters/day	Average	27 (13)	26 (17)	34 (15)	30 (13)
		Range	0-83	0-75	0-70	0-52
3	10% dextrose in water, 2 liters/day	Average	21 (15)	24 (19)	29 (15)	24 (10)
		Range	0-72	0-88	0-91	0-99
4	5% dextrose in 5% amigen ● or Merck amino acids, 2 liters/day	Average	22 (9)	24 (9)	9 (9)	9 (9)
		Range	1-43	9-46	0-14	0-17
5	10% dextrose in 5% amigen ● and 5% alcohol, 2 liters/day	Average	27 (4)	43 (4)	33 (4)	38 (4)
		Range	18-44	31-54	18-53	31-47

* The numbers in parentheses refer to the number of patients.

TABLE 2.—*Preoperative and Postoperative Glycosuria (Grams/Twenty-Four Hours)*

	Preoperative and Postoperative Days									
Case	—5	—4	—3	—2	—1	1	2	3	4	5
1	..	..	..	17	22	42	12	16	17	36
2	..	..	..	13	13	45	9	49	26	..
3	..	..	..	5	12	12	26	6	12	..
4	..	..	..	34	35	21	49	52	32	40
5	..	..	..	10	5	7	20	32	14	..
6	..	..	7	10	21	40	41	56	18	..
7	..	..	16	5	6	6	35	12	45	7
8	..	..	10	10	8	10	13	10	10	14
9	..	..	23	31	44	37	41	24	41	..
10	..	..	13	0	0	43	38	11	17	..
11	..	0	0	0	0	21	25	16	17	..
12	..	5	7	10	8	16	31	0	0	9
13	..	9	7	7	6	41	17	15	10	..
14	14	20	33	12	22	8	11	14	17	10
15	13	0	0	0	0	21	25	16	17	..

tained acetone. In five other patients, all given dextrose at the approximately same rate after operation, the following average values for glycosuria (in grams) were obtained on each of the four postoperative days: 14, 38, 45 and 33. The data in the chart, and the figures in table 1 also suggest an increased degree of glycosuria on the second and third postoperative days.

In three patients a study was made of the so-called Staub effect during the postoperative period. According to Staub and others, an initial infusion of dextrose at a slow rate enables the body to assimilate glucose subsequently at a higher rate. This observation has been applied clinically as a means of increasing the rate of assimilation of intravenously administered dextrose.[8] The effect, it should

be emphasized, has been observed only in normal persons. We found no evidence of a "Staub effect" during the postoperative period. In none of the three patients did the preliminary infusion of dextrose at a slower rate diminish the tendency toward glycosuria subsequently, compared with control observations made the previous or subsequent day with dextrose given at a constant rate.

Diuresis.—From the differences in the amount of glucose lost, one might expect evidence of considerably greater 24 hour urinary output in patients given 10 per cent solutions as compared with those given 5 per cent solutions. This was not the case. Study of the variations in the two groups revealed no statistical difference. Attempts to correlate the 24 hour volume of urine with the degree of glycosuria were likewise unsuccessful. Moreover, no influence of added salt was apparent.

Because glycosuria has long been known to induce an increased output of urine, observations were made in several patients in whom the 24 hour urinary output was collected in two fractions, one during the day while the intravenous injections

TABLE 3.—*The Correlation Between Glycosuria and Diuresis*

Duration of Infusion, Hours	Glucose Excreted, Gm.		Urinary Output, Ml.	
	7:00 a. m.-7:00 p. m.	7:00 p. m.-7:00 a. m.	7:00 a. m.-7:00 p. m.	7:00 p. m.-7:00 a. m.
4.75	86	4	1,080	120
5.0	54	30	1,080	500
4.75	83	10	1,580	250
4.25	69	28	1,200	460
0.0	0	0	1,780	605
7.0	8	2	1,960	330
7.25	4	1	1,570	180
5.0	36	2	1,020	200
7.5	6	2	430	255
4.75	21	2	1,040	290
5.0	6	4	840	365
4.75	45	3	1,800	270

were given, and the other during the night after the injections had been finished. The findings are shown in table 3. The striking differences observed are also illustrated in the following two patients, each given 2 liters of 10 per cent dextrose during the daytime hours, the injection of the first liter starting some time after 7:00 a. m. and injection of the second liter ending by 6:00 p. m. The duration of each injection was two to four hours. One patient during three preoperative days excreted 134, 124 and 130 cc. per hour from 7:00 a. m. to 11:00 p. m., in contrast to 27, 20 and 15 cc. per hour from 11:00 p. m. to 7:00 a. m. Another patient during four postoperative days excreted 140, 90, 126 and 100 cc. per hour from 8:00 a. m. to 8:00 p. m., in contrast to 10, 40, 20 and 40 cc. per hour from 8:00 p. m. to 8:00 a. m. Thus it would seem that while single intravenous injections of dextrose may lead to a pronounced diuresis, the effect is transient and the excessive loss of water is compensated by a subsequent period of oliguria. Scrutiny of the data in table 3 also shows fairly close correlation in many cases between diuresis and the amount of glucose excreted.

Acetonuria.—Acetonuria was detected in only 73 of 359 specimens, or 20 per cent, the incidence being the same for those obtained from females as for those obtained from males. However, analysis of individual patients showed that of the

57 female patients studied, 21 or 37 per cent had acetone in one or more specimens of urine, whereas of 21 male patients studied, only 6 or 28 per cent showed acetone. There was no difference in the incidence of acetonuria between the preoperative and postoperative periods. Analysis of the incidence on each postoperative day showed only a slight decrease on the first day as compared with the second, third and fourth days after operation.

There was a striking difference in acetonuria between those receiving 10 per cent dextrose and those receiving the 5 per cent solution. Thus of 185 twenty-four hour urine specimens obtained from patients given 10 per cent dextrose, only 10 (or 5 per cent) were positive, whereas of 58 similar specimens from patients given 5 per cent dextrose, 14 (or 24 per cent) were postive. However, the highest incidence of acetonuria occurred in patients receiving amino acids; of 98 specimens, 44, or 45 per cent, were positive. This finding is discussed in detail later. This fact was also true, though to a lesser extent, of patients given the highest caloric intake (with 5 per cent alcohol), who showed an incidence of acetonuria of 28 per cent (5 of 18 specimens).

The relationship between acetonuria and glycosuria was scrutinized, but no significant correlation could be established except for the greater incidence of the

TABLE 4.—*Total Ketone Bodies in Urine*

Patient	Date 7:00 a. m.-7:00 p. m.	Urinary Volume, Liters	Total Ketone Bodies	
			Gm./Liter	Total, Gm.
Mc	10/4 - 5	1.22	0.535	0.653
Mc	10/5 - 6	1.66	1.882	3.124
Mc	10/6 - 7	2.41	0.233	0.56
Ma	10/6 - 7	1.08	0.731	0.790
Ma	10/7 - 8	1.40	0.607	0.850
Th	11/23-24	0.95	0.804	0.763
Fr	11/24-25	0.90	0.555	0.499

latter than of the former (78 per cent and 20 per cent), as already mentioned. Of the 494 specimens examined, only 39 showed neither acetonuria nor glycosuria, of which eight were preoperative specimens. In only six specimens was acetonuria found without glycosuria, equally divided between preoperative and postoperative specimens.

Thus, of 68 specimens showing acetonuria, all but six also contained glucose. Moreover, acetone was observed in several patients during the daytime hours, when diuresis and glycosuria were pronounced, whereas none was found in the urine excreted during the night hours, when glycosuria was absent. This unusual finding might have been more frequent had more fractional specimens of urine been studied.

The actual amount of ketone bodies excreted in the urine of the patients in this investigation was measured in seven specimens showing a 4 plus value (table 4). Obviously the specimens showing 1 plus, 2 plus and 3 plus values would contain less than this maximum amount. In the specimens which had shown a 4 plus value analysis revealed a maximum amount of ketone bodies of 3.1 Gm. The actual figures, as shown in table 4, agree rather well with the findings of Roscher [2] and Heidecker,[5] as already mentioned. As might therefore be expected from the

small amount of ketone bodies excreted, we found no fall in the carbon dioxide-combining power in any of our cases after four or more days of intravenous subcaloric intake.

COMMENT

In commenting on the present findings, the question, suggested in the title to this paper, may be asked: What is the significance of acetonuria and glycosuria after operation? In discussing this question, it is of value to consider two periods, the first consisting of the time occupied by the operation, ending about 24 hours later, the second consisting of the succeeding days. The first period would thus show the effect of the immediate influence of operative trauma, especially of anesthesia. The second period would reveal the ultimate metabolic effects of trauma and anesthesia, especially as influenced by the nutritional intake during the immediate postoperative period.

From the present findings as well as the observations made by others, it would seem that glycosuria and acetonuria are less pronounced (in patients on an adequate preoperative caloric intake) during the first 24 hours compared with subseqent periods of observation. This conforms with most studies, which agree that the effects of operation on carbohydrate metabolism are transient and not intense. For example, the rise in blood sugar is all but spent by six, and at most 24, hours after operation, and one would therefore not expect much glycosuria even if one considered the well known effect of general anesthetic agents in promoting glycogenolysis. Indeed, sugar tolerance tests [19] 15 hours after operation have shown no significant change. As far as acid-base balance is concerned, anesthesia produces a transient disturbance which is probably largely of respiratory origin and not due to an increase in ketone body formation during this period.

During the succeeding days after operation, glycosuria and acetonuria are best discussed separately. In general, the former is the result of rapid intravenous infusion and the second the result of a subcaloric intake.

Glycosuria.—It seems clear from previous studies that postoperative glycosuria is not found unless dextrose is given intravenously. Several observers have shown that when the intake is all oral or when the parenteral intake is limited to water and salt, accidental injury (aside from head injuries) or operation is not followed by glycosuria. It may be inferred, therefore, that in the present study glycosuria is directly connected with the rate of intravenous administration of dextrose. It is likely, however, that the degree of glycosuria is also related to a diminution in the normal rate of peripheral utilization. Although not striking, there was a tendency toward an increased glycosuria on the second or third days which would seem to be connected with the effect of the so-called alarm reaction, i. e., an increased adrenal-pituitary secretion of hormones, which also reaches its metabolic peak on the second to the fourth day after stress.

The relationship between glycosuria and the rate of infusion may be discussed in some detail. About 35 years ago careful studies by Woodyatt and his co-workers [14] on the normal human adult showed that glycosuria appeared when the rate of intravenous infusion exceeds 0.9 Gm. of dextrose per kilogram per hour. However, this figure was determined only after using a preliminary "priming" period, during which the body developed a greater degree of assimilation (Staub effect, see below) and thus tolerated a more rapid intravenous infusion without

glycosuria. This rate has long been accepted as the maximum for proper infusion. However, if one does not employ a preliminary priming period and starts and maintains the intravenous infusion at a uniform rate, as is the case with the usual clinical administration of dextrose, a much lower figure is obtained for the rate of injection above which glycosuria appears. This rate is probably about 0.5 Gm. per kilogram per hour.[21] During the postoperative period, however, glycosuria will occur even when the dextrose is injected at a much lower rate, 0.25 Gm. per kilogram per hour.[22] In the study by Pareira and Somogyi[8] it was recommended that the rate of dextrose infusion be kept low during the first hour or even half hour; they were thereby able to increase the infusion "to a rate of 50 grams per hour," or about 0.6 to 0.9 Gm. per kilogram per hour with little or no glycosuria. This so-called Staub effect, however, was not observed by us. As stated in our findings, we found no evidence that such a preliminary slow infusion was followed by an increased rate of assimilation during the postoperative period.

The aforementioned rates of infusion are all based on the concept of the maximum rate of utilization without glycosuria. Yet there is evidence that the body can assimilate glucose at a much higher rate provided one does not try to prevent glycosuria. Indeed, a high blood sugar level, even though it leads to glycosuria, has the advantage of promoting a higher rate of glucose retention, which thus leads to a higher level of hepatic glycogen, an objective which has clinical value. By accepting glycosuria, one may provide the patient with much more carbohydrate food in the same period. For example, a rapid infusion of dextrose, 1 Gm. per kilogram per hour, could lead to the loss of 0.2 Gm. per kilogram per hour in the urine, or the retention and utilization of 0.8 Gm. per kilogram per hour. To prevent glycosuria, one might have to lower the rate to 0.4 Gm. per kilogram per hour in the same patient. Thus it is obvious in such a case that half as much glucose is retained and utilized per unit time by the patient if glycosuria is avoided. This point of view has been overlooked by most workers in the field.

Cain and Belk[23] have studied this problem in some detail. In a series of patients given intravenous injections of dextrose, they noted that in general the amount of glucose retained per hour was directly proportional to the amount given per hour. They proposed, therefore, that one disregard glycosuria in order to attain the maximum amount of glucose assimilation in the shortest time. Unfortunately, their observations were limited to single injections and the greatest amount of dextrose given was 150 Gm. Although the maximum rate of infusion was 20 Gm. per kilogram per hour, only 25 Gm. were injected in this case, i. e., 50 cc. of a 50 per cent solution. Of this, nearly 10 per cent was lost in the urine. In another case, 500 cc. of 20 per cent dextrose was given at a rate of 6.6 Gm. per kilogram per hour, and of this 100 Gm., or 12 per cent, was lost in the urine. Curiously enough, the greatest loss in the urine was 58 per cent of that injected in a patient given 150 Gm. as 3 liters of a 5 per cent solution at a much slower rate (0.88 Gm. per kilogram per hour). Of 22 experiments, 6 were followed by a loss

21. Lockhart, C. E., and Elman, R.: The Effect of Intravenous Glucose and Amino Acids on Glycosuria and Urinary Output in Humans, Surg., Gynec. & Obst. **88**:97, 1949.

22. Winslow, S.: Dextrose Utilization in Surgical Patients, Surgery **4**:867, 1938. Elman and others.[1] Lockhart and Elman.[21]

23. Cain, J. C., and Belk, W. P.: The Assimilation Rate of Intravenously Injected Glucose in Hospital Patients, Am. J. M. Sc. **203**:359, 1942.

of 20 per cent or more of the amount of dextrose injected and 11 by a loss of 10 per cent or more. However, the author mentioned no data on the diuresis produced by these rapid rates of infusion.

If glycosuria of itself insures the most rapid assimilation and utilization of glucose, is it otherwise harmful? The loss of glucose itself is probably of no importance since glucose is inexpensive and easy to give. However, it should be remembered that the degree of glucose wastage may be considerable. For example, in the present study, as much as 25 to 50 per cent of the injected dextrose was lost in some cases. Calculations based on the caloric value of the injected dextrose will be in error to that extent. More important than the loss of glucose is the inevitable diuresis which is associated with glycosuria.

Based on studies of the 24 hour intake and output, the present findings showed no evidence of dehydration following the intravenous injection of dextrose. However, this is true only because the loss of water which occurs during the intravenous infusion is usually balanced by a compensatory oliguria during the subsequent period when no dextrose is given. Thus the total urinary output is the same. However, the dehydration which necessarily occurs during the six to 10 hours of infusion may be harmful in a very sick patient. Moreover, it is unlikely that the surgeon will be aware of it.

Recent data from this laboratory [24] have shown that fructose is much less likely to lead to glycosuria and diuresis than dextrose. Its more rapid rate of assimilation after intravenous injection would seem to obviate many of the objections to rapid infusion of dextrose.

The effect of giving amino acids on glycosuria is hard to evaluate on the basis of the present findings (table 1). The loss with 5 per cent dextrose and 5 per cent amino acids (group 4) is about the same as that with 10 per cent dextrose (groups 2 and 3) on the first two postoperative days, but on the third and fourth days the loss is much smaller and indeed is about the same as that with 5 per cent dextrose alone (group 1). These findings cannot be used to support the idea of Lockhart and Elman [21] that glucose utilization is improved by adding amino acids to the intravenously administered dextrose. Adding 5 per cent alcohol (to 10 per cent dextrose and 5 per cent amino acids) led to glycosuria which was no greater than that which might have occurred with 10 per cent dextrose alone (group 5, table 1). Without data on the losses of alcohol, it is impossible to draw any inferences in regard to the preferential use of alcohol and dextrose as a source of energy when both are available at the same time. However, the findings show that the addition of alcohol does not materially decrease the assimilation of glucose.

One may state in summary that postoperative glycosuria in itself may be a desirable phenomenon in so far as it assures the highest rate of glucose assimilation. However, its dehydrating effect during infusion cannot be accepted complacently, particularly in very sick patients. This dehydration may be combated, of course, by the administration of more fluids or by a slower rate of injection. However, this detracts from the advantages of giving the infusion in a shorter time. This dilemma may be solved by the use of 10 per cent fructose solutions.[24]

24. Weichselbaum, T. E.; Elman, R., and Lund, R. H.: The Comparative Utilization of Fructose and Glucose Given Intravenously, Proc. Soc. Exper. Biol. & Med. **75**:816, 1950.

Ketonuria.—Ketone bodies (acetoacetic acid, acetone, betahydroxybutryic acid) are readily utilized by the peripheral tissues as a source of energy under practically all known conditions. Indeed, 50 to 80 per cent of the total oxygen consumption may come from the burning of ketone bodies.[18] An increased production of ketone bodies is normal whenever the caloric intake is inadequate and metabolism is otherwise normal. This is true because the body then uses its adipose tissue for energy, a process which involves the conversion of fatty acids to ketone bodies by the liver. Thus the production of ketone bodies by the liver necessarily increases whenever a large part of the energy comes from fat. Should the production of ketone bodies exceed the ability of the peripheral tissues to burn them, the blood level rises (ketonemia) and ketonuria becomes inevitable (even though the actual amount wasted is not large). The more glucose available for energy, the less fat is burned, and hence ketonuria is less likely; glucose is therefore said to be the best antiketogenic substance. Ketone bodies may also originate from a few of the amino acids such as leucine, isoleucine, phenylalanine and tyrosine. This may explain the high incidence of acetonuria found after intravenous infusion of amino acids in the present study.

The degree of ketonuria which occurs in the normal person with a subcaloric intake is seldom pronounced, although it may reach up to 15 Gm. per day after complete starvation.[4] In severe diabetic coma, the amount of ketone bodies excreted in the urine can reach 20 to 30 Gm. per day. Such an amount indicates a high blood ketone level, about 80 mg. per 100 cc., or 80 times the normal value of 1 mg. per 100 cc. Since the ketone bodies are acidic in nature, they are neutralized by sodium bicarbonate and excreted in the urine as sodium salts. Thus in severe diabetic coma, the body is depleted of sodium and a state of acidosis is produced.

When the missing energy needs of the patient on the subcaloric intake are supplied wholly by his body fat, no physiological impairment follows inasmuch as adipose tissue is a true store of food and has little or no other function. By contrast, when the missing calories are wholly supplied by the protein tissue, excessive nitrogen is lost in the urine and physiological impairment may follow. Actually, both tissues are used during the period of subcaloric intake. However, utilization of adipose tissue for energy is apparently inhibited by increased adrenocortical activity (which is known to occur during trauma), as shown by experiments indicating that cortisone has such action[25] and by experiments on the ketosis of fasting, which is diminished by adrenalectomy.[10] The same inference follows consideration of the study of Roscher, already mentioned, in which the degree of ketonuria was much less in postoperative patients when compared with the control patient not operated on and given the same dietary intake. Indeed, this experiment showed that the amount of nitrogen excreted after operation was much greater than that in the control case, which fits the old observation that adrenocortical hormones increase protein tissue breakdown, which in turn also yields calories. In the postoperative patient on a subcaloric intake, therefore, the comparative urinary content of ketone bodies and of nitrogen gives a relative measure of the amount of adipose and protein tissue, respectively, used to supply missing calories. The loss of fat is much to be preferred to the loss of protein in

25. Stoerk, H. C., and Porter, C. C.: Prevention of Loss of Body Fat by Cortisone, Proc. Soc. Exper. Biol. & Med. **74**:65, 1950.

terms of resultant physiological impairment. On the basis of these considerations, ketonuria in the degree observed may be looked on as a favorable finding in that it implies utilization of adipose tissue for the missing calories.

As far as producing acidosis is concerned, the quantitative studies presented herein show that the ketonuria observed was always so insignificant in degree as to lead to no such danger. As compared with that excreted in complete starvation, the amount was small. Thus in all but one specimen the total excretion was less than 1 Gm. and indeed was probably less than 100 mg. in the vast majority of cases. With an over-all incidence of acetonuria of only 20 per cent of all specimens examined, it may be stated that with an intake of 100 Gm. of dextrose or more, ketosis was not a significant finding in the type of surgical patients here studied. Moreover, the absence of any change in the carbon dioxide-combining power during the postoperative period lends support to this inference.

SUMMARY

Glycosuria was found in 78 per cent of preoperative and postoperative specimens in patients receiving 5 or 10 per cent dextrose with or without added amino acids, alcohol or salt. The degree and incidence were slightly greater after operation, especially on the second and third days, than before. There was no evidence of increased glycosuria on the day of operation. Glycosuria tended to be greater with increased rates of infusion. The actual amounts of glucose lost varied but were surprisingly large, reaching a maximum of 25 per cent of that injected with an intake of 100 Gm. a day and of 50 per cent of that injected with a daily intake of 200 Gm.

Diuresis accompanied glycosuria during the periods of infusion but was compensated by subsequent oliguria during the period when no infusions were given. This transient dehydration may be harmful in certain patients.

Acetonuria was found in but 20 per cent of all specimens and showed no difference in incidence before or after operation. It was more frequent in females than in males, more frequent with a 100 Gm. dextrose intake than with 200 Gm. and much more frequent after the injection of amino acids. The total amount of ketone bodies excreted was always small, not exceeding 1 Gm. each 24 hours in all but one specimen and being probably less than 200 mg. in the rest. This degree of ketonuria is considered of little or no significance in leading to a disturbance of acid-base balance. It is probably only indicative of a subcaloric intake and of the fact that adipose tissue is supplying calories for basic metabolic needs.

No evidence was found in the postoperative period that the rate of glucose assimilation could be increased by a preliminary infusion of dextrose at a slower rate.

It is inferred from the present study that there is little evidence of a serious disturbance in the carbohydrate metabolism in nondiabetic adults subjected to major surgical procedures and receiving feedings intravenously. However, the degree of glucose loss may reach 25 to 50 per cent of that injected. Excessive glycosuria may be harmful by producing transient dehydration.

CORONARY THROMBOSIS AND INSUFFICIENCY RESULTING FROM SHOCK

A Clinical and Pathologic Study

HARRY A. DAVIS, M.D.
VINCENT J. PARLANTE, M.D.
AND
ALVERTA M. HALLSTED, M.D.
LOS ANGELES

THE SIGNIFICANCE of arterial and venous thrombosis and of thromboembolism as complications of shock has been recently emphasized.[1] Thrombosis may develop in any blood vessel and frequently is not recognized because it occurs in vessels which do not serve vital areas or tissues or because the thrombus does not become detached to form an embolus. The sites of formation which are most likely to be recognized clinically are the venous system of the lower extremities, the coronary arteries,[2] the cerebral blood vessels and the vessels of the retina.

From the Los Angeles County General Hospital and the Department of Surgery, College of Medical Evangelists, Los Angeles Division.

1. Davis, H. A.: Shock and Allied Forms of Failure of the Circulation, New York, Grune & Stratton, Inc., 1949.

2. (*a*) Randall, O. S., and Orr, T. G.: Post-Operative Coronary Occlusion, Ann. Surg. **92**:1014-1018 (Dec.) 1930. (*b*) Menard, O. J., and Hurxthal, L. M.: Painless Coronary Thrombosis as Postoperative Complication, S. Clin. North America **11**:395-401 (April) 1931. (*c*) De Santo, D. A.: Operation and Trauma as Cause of Coronary and Cerebral Thrombosis, Am. J. Surg. **26**:35-42 (Oct.) 1934. (*d*) Bean, W. B.: Infarction of the Heart: A Morphological and Clinical Appraisal of 300 Cases; Predisposing and Precipitating Conditions, Am. Heart J. **14**:684-702 (Dec.) 1937. (*e*) Meessen, H.: Über Coronarinsuffizienz nach Histamincollaps und nach orthostatischem Collaps, Beitr. z. path. Anat. u. z. allg. Path. **99**:329-350, 1937 (*f*) Boas, E. P.: Coronary Artery Thrombosis as Delayed Postoperative Complication, J. Mt. Sinai Hosp. **4**:923-927 (March-April) 1938. (*g*) Master, A. M.; Dack, S., and Jaffe, H. L.: Postoperative Coronary Artery Occlusion, J. A. M. A. **110**:1415-1418 (April 30) 1938. (*h*) Horn, H.; Dack, S., and Friedberg, C. K.: Cardiac Sequelae of Embolism of the Pulmonary Artery, Arch. Int. Med. **64**:296-321 (Aug.) 1939. (*i*) Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, J. A. M. A. **112**:1675-1679 (April 29) 1939. (*j*) McLaughlin, C. W.; Baker, C. P., and Sharpe, J. C.: Bleeding Duodenal Ulcer Complicated by Myocardial Infarction, Nebraska M. J. **25**:266-268 (July) 1940. (*k*) Master, A. M., and Jaffe, H. L.: Coronary Insufficiency and Myocardial Necrosis Due to Acute Hemorrhage in Ulcerative Colitis, J. Mt. Sinai Hosp. **7**:26-28 (May-June) 1940. (*l*) Blumgart, H. L.; Schlesinger, M. J., and Zoll, P. M.: Multiple Fresh Coronary Occlusions in Patients with Antecedent Shock, Arch. Int. Med. **68**:181-198 (Aug.) 1948. (*m*) Boas, E. P.: Some Immediate Causes of Cardiac Infarction, Am. Heart J. **23**:1-15 (Jan.) 1942. (*n*) Kinney, T. D., and Mallory, G. K.: Cardiac Failure Associated with Acute Anemia, New England J. Med. **232**:215-218 (Feb. 22) 1945. (*o*) Cameron, D. R.: Transient Heart Block and Coronary Occlusion in Pleural Shock, Brit. Heart J. **7**:104-106 (April) 1945.

The purpose of this paper is to present a study of the cases of coronary thrombosis and insufficiency resulting from shock which were observed in the Los Angeles County General Hospital from 1942 to 1949.

PRESENT SERIES OF CASES

The case records of 3,365 patients at the Los Angeles County General Hospital with a diagnosis of coronary thrombosis were reviewed. The period covered was from January 1942 to July 1949. During this interval of seven and one-half years, there were 18 cases of coronary thrombosis following shock and proved by autopsy (table 1). In 22 additional cases, coronary thrombosis was associated with antecedent shock, but the diagnosis was made on the basis of clinical or electrocardiographic findings and was not confirmed by autopsy studies.

STATISTICAL ANALYSIS

There were 18 patients in this series, of whom 14 were men and four women. It is of interest that the 10 patients in whom coronary occlusion or insufficiency followed surgical operation were all of the male sex. The ages ranged from 45 to 80 years, and the majority of the patients were between 50 and 60 years and between 70 and 80 years. The age distribution was as follows: Two were 40 and 49 years, 7 between 50 and 59 years, 2 between 60 and 69 years and 6 between 70 and 79 years, and 1 was 80 years old. The average age was 69.4 years.

Shock was caused by surgical operation in four patients, surgical operation and anesthesia in five, postoperative peritonitis in two, accidental trauma in one, thermal trauma (burns) in one, insulin in one (a diabetic patient), barbiturate poisoning in three, and arsenic poisoning in one.

Of the 10 patients subjected to surgical operation, the anesthetic used was not stated in 3, cyclopropane was used in 1, refrigeration in 1 and spinal anesthesia in 5.

The duration of the shock episode was variable and ranged from 30 minutes to 96 hours. In three patients the duration of the shock episode could not be ascertained with any accuracy. Among the remaining 15 patients, the duration of the shock episode was 12 hours or less in eight patients and more than 12 hours in 7. The duration periods and their distribution were as follows: 30 minutes (three patients); one hour (one patient); four and one-half hours (one patient); seven hours (one patient); 10 hours (one patient); 12 hours (one patient); 16 hours (one patient); 19 hours (one patient); 24 hours (one patient); 30 hours (one patient); 43 hours (one patient); 45 hours (one patient), and 96 hours (one patient).

The interval of time which elapsed between the shock episode and the time of the patient's death was likewise variable and ranged from one hour to 12 days. The average time interval was 68.8 hours. In eight of the 18 patients the time interval was 24 hours or less, and in 15 of the 18 patients it was 96 hours or less. Only three of the 18 patients died more than 96 hours after the shock episode.

Prior clinical evidence of coronary disease was absent in 14 patients, present in two patients and not stated in two patients. However, pathologic evidence of coronary disease was observed in 14 of the 18 patients. In the remaining 4 patients the presence or absence of coronary disease was not stated.

TABLE 1.—*Coronary Thrombosis and Insufficiency Resulting From Shock*

Patient	Age	Sex	Cause of Shock	Duration of Shock, Hr.	Survival Period, Hr.	Precordial Pain	Coronary Arteriosclerosis	Coronary Thrombosis	Myocardial Infarction	Site of Coronary Thrombosis and Stenosis
1	70	Male	Surgical	0.5	72	None	Present	Absent	Present	Not stated
2	47	Male	Postoperative peritonitis	96	96	None	Present	Present	Present	Anterior descending left coronary
3	79	Male	Surgical	?	240	None (?)	Present	Present	Present	Right coronary
4	69	Male	Surgical	0.5	96	None	Present	Absent	Present	Right coronary
5	64	Male	Surgical	24	24	None (?)	Present	Present	Present	Anterior descending left coronary
6	50	Male	Spinal anesthesia	4.5	4.5	None	Present	Present	Absent	Left coronary
7	51	Male	Spinal anesthesia	7	22	None	Present	Present	Absent	Circumflex branch of left coronary
8	72	Male	Surgical and spinal anesthesia	12	69	Present	Present	Present	Present	Descending branch of left coronary
9	55	Male	Spinal anesthesia	1	1	None (?)	Present	Present	Absent	Right coronary
10	72	Male	Surgical and spinal anesthesia	0.5	288	None	Present	Present	Present	Left coronary
11	52	Male	Burns	43	43	None	?	Present	Absent	Left coronary
12	80	Female	Accidental trauma	30	156	Present	Present	Present	Absent	Posterior branch of left coronary
13	54	Female	Insulin	10	24	Present	Present	Absent	Present	Right and left coronaries
14	70	Male	Arsenic poisoning	16	16	None (?)	?	Present	?	Circumflex branch of left coronary
15	53	Male	Barbiturate poisoning	45	24	None (?)	?	Present	Present	Circumflex branch of left coronary
16	45	Female	Barbiturate poisoning	?	72	None (?)	?	Present	Present	Left coronary
17	77	Female	Barbiturate poisoning	?	96	None (?)	Present	Present	Absent	Descending branch of left coronary
18	53	Male	Postoperative peritonitis	19	19	None	Present	Present	Present	Right coronary

The site of the coronary lesion was the left coronary artery in 12 patients, the right coronary artery in four patients and the right and left arteries in one patient. In one patient the site of the coronary lesion was not stated. Myocardial infarction was present in 11 patients, absent in six and not stated in 1. Coronary thrombosis was present in 14 patients and absent in four patients. Coronary thrombosis and myocardial infarction occurred together in seven patients. However, in six patients there was coronary thrombosis but no myocardial infarction. In three patients myocardial infarction was associated not with coronary thrombosis but the coronary stenosis (coronary insufficiency).

COMMENT

Shock has been defined as "a state involving the entire organism, characterized by a generalized impairment of the circulation, and caused by any form of stress or injury which reduces the output of blood from the left ventricle of the heart to a level below that needed for normal cellular function and metabolism."[1] The mechanisms underlying the reduction of the output of blood from the left ventricle may be placed in the following two categories: (1) decrease in the venous return to the left side of the heart due to (*a*) diminished blood volume (trauma, hemorrhage, burns), (*b*) segregation of blood in the capillaries, (*c*) segregation of blood in the venous system, (*d*) mechanical obstruction to the venous return, (*e*) loss of inspiratory suction effect, (*f*) failure of the right side of the heart or (*g*) obstruction to the pulmonary arterial flow; (2) inadequacy of function of the left side of the heart due to (*a*) decreased ability of the left side of the heart to expel blood into the arterial system (late stages of heart failure, myocardial infarction, ventricular fibrillation, etc.) or (*b*) decreased diastolic filling of the heart (extreme tachycardia, cardiac tamponade).

The incidence of shock as an etiologic factor antecedent to coronary thrombosis and insufficiency has been variously estimated as follows: 3.3 per cent in 300 cases[2d]; 3.3 per cent in 625 cases[2g]; 8.8 per cent in 350 cases.[21] In the present series of 3,365 patients there was an incidence of 0.5 per cent proved cases and of an additional 0.6 per cent of probable cases in which coronary thrombosis or insufficiency was precipitated by shock.

Why coronary thrombosis and insufficiency occur as a result of shock is unknown, but mechanisms which have been suggested are impaired nutrition and increased permeability of the coronary arterial walls, slowing of the blood flow through the vessels, lowering of the arterial pressure within the coronary vessels and increased tendency to clot formation and to "sludging" of the red blood cells. In hemorrhagic shock the coronary blood flow is reduced from 30 to 60 per cent and the coronary vessels dilate as is shown by a decrease in flow resistance. The administration of blood and plasma transfusions affect the coronary blood flow in shock. In hemorrhagic shock, blood transfusions will greatly increase the reduced coronary blood flow, and this increase is maintained for a prolonged period.[3] In the present series of 18 patients no transfusions were given to seven (table 2). Only four patients received transfusions (blood or plasma) of 1,000 cc.

3. Opdyke, D. F., and Foreman, R. C.: A Study of Coronary Flow Under Conditions of Hemorrhagic Hypotension and Shock, Am. J. Physiol. **148**:726-739 (March) 1947.

or more. This inadequate replacement of the blood volume when it is reduced may be responsible in part for the onset of coronary thrombosis or insufficiency by permitting the continued existence of a state of reduced coronary blood flow. Ephedrine was administered to many of the patients in this series in an effort to elevate the blood pressure. It is the consensus that the predominant effect of ephedrine on the coronary vessels is one of vasodilatation accompanied with a considerable increase in coronary blood flow.

Precordial pain is noteworthy by its infrequency in these patients. In the present series there was no relationship between the presence or absence of precordial pain and the presence or absence of coronary thrombosis or myocardial infarction. Of the 18 patients, precordial pain was definitely stated to be absent in seven and to be present in three. There was no statement made concerning precordial pain in the remaining eight patients. Presumably, it was either absent or

TABLE 2.—*Blood Transfusions in Shock Complicated by Coronary Thrombosis and Insufficiency*

Case	Cause of Shock	Blood, Cc.	Plasma, Cc.
1	Surgical	500	0
2	Postoperative peritonitis	1,000	0
3	Surgical	0	0
4	Surgical	0	0
5	Surgical	1,000	0
6	Spinal anesthesia	0	500
7	Spinal anesthesia	500	250
8	Surgical and spinal anesthesia	500	0
9	Spinal anesthesia	0	0
10	Surgical and spinal anesthesia	0	0
11	Thermal burns	0	3,500
12	Accidental trauma	500	250
13	Insulin hypoglycemia	0	500
14	Arsenic poisoning	500	0
15	Barbiturate poisoning	0	0
16	Barbiturate poisoning	0	0
17	Barbiturate poisoning	0	0
18	Postoperative peritonitis	1,500	500

was not severe enough to be called to the physician's attention. A survey of the reported cases reveals the fact that precordial pain is usually not present. This absence of pain may be attributed, in part at least, to clouding of the sensorium either by shock or by the coincidental administration of narcotic drugs.

While there does not seem to be any particular operation which is likely to be followed by coronary thrombosis or insufficiency, it would seem that in this series of cases and in the cases reported in the literature transurethral resection of an enlarged prostate gland is frequently followed by this complication. Herniorrhaphy is also a frequent cause of this complication. This fact may be attributable not to the operative procedure itself but rather to the fact that spinal anesthesia, which is often used for this operation, is the cause of acute hypotension in these patients. Other operative procedures not infrequently followed by shock and coronary thrombosis are those performed in the upper region of the abdomen, particularly operations on the gallbladder and the stomach. Thyroid operations also have been followed by shock and coronary thrombosis or insufficiency.

Is the type of anesthesia related etiologically to this complication? We have received the distinct impression that spinal anesthesia, particularly when induced in patients with arteriosclerosis and/or hypertension, has been followed by a disproportionately frequent occurrence of this complication. In the present series there were 10 surgical cases, and in five of these spinal anesthesia was used, in one cyclopropane, in one refrigeration anesthesia, and in three the form of anesthesia used was not stated. In reviewing the literature we could find only 38 cases in which reference was made to the type of anesthetic employed; spinal anesthesia was used in 14 patients and local anesthesia in 13 and various general anesthetic agents were used in 11 patients.

There is no conclusive evidence regarding the effect of early ambulation on the postoperative incidence of this condition. In the cases reported by Master and his co-workers [28] early ambulation after operation did not prevent the occurrence of coronary thrombosis.

What is the reason for the latent period between the shock episode and the time of death? We have already indicated that in the series of patients under discussion the period ranged from one hour to 12 days and that the average interval of time which elapsed was 68.8 hours. In 44 per cent of the patients the time interval was 24 hours or less, and in 83.2 per cent it was 96 hours or less. Relatively little attention has been paid to this matter in the literature. In 35 cases of postoperative coronary occlusions reported by Master and his associates [28] the interval varied from four hours to 21 days. The latent interval may be explained in three ways: 1. The thrombotic lesion in the coronary artery may be initiated during the period of shock and thereafter may produce complete arterial occlusion either rapidly (as in case 9 in one hour) or slowly over a period of days. 2. The thrombotic lesion may not start during the period of shock but later during the postshock phase. 3. Myocardial infarction in the absence of coronary thrombosis may occur over a period of hours or days.

The duration of the shock episode and of the interval of time which elapses between the onset of shock and the death of the patient appears to influence the character of the cardiac lesion. In general, the longer the duration of shock the more likely is coronary thrombosis to be found at autopsy. In this series of 18 patients the duration of shock was known in 15. When shock had lasted less than one hour (three patients), coronary thrombosis was absent in two patients. The longer the survival period after the shock episode, the higher was the incidence of myocardial infarction. Thus, among the patients who survived the shock episode for a period of one day or longer (13 patients), myocardial infarction was observed at autopsy in 10. Of the five patients who survived less than 24 hours after the shock episode, three did not exhibit myocardial infarction at postmortem examination, one had myocardial infarction and in one myocardial infarction was probably absent. Thus, one may conclude that with certain exceptions the duration of the shock episode determined the frequency of occurrence of coronary thrombosis while the length of the survival period after shock influenced the incidence of myocardial infarction. These facts may be explainable on the basis that the thrombotic lesion develops relatively rapidly while the myocardial lesion requires a longer time for its pathologic evolution.

The character of the lesions in the coronary vessels and in the myocardium has been discussed earlier. The coronary occlusion was caused by thrombosis in 15 patients and by arteriosclerotic narrowing in three patients. In none of the patients in this series was there present the coronary lesion of the type described by Paterson,[4] in which the occlusion is produced by hemorrhage into an arteriosclerotic plaque. This fact coincides with the observation of Friedberg and Horn,[21] who in 34 instances of myocardial infarction did not find the Paterson type of coronary occlusion. Myocardial infarction associated with coronary stenosis occurred in three of the 18 patients in this series. In all these patients the coronary arteries were greatly narrowed as a result of arteriosclerosis. The myocardial infarction in such circumstances is due partly to the coronary stenosis and partly to the fall in coronary blood pressure. Shock, with a fall in the general arterial blood pressure, may produce myocardial infarction even when coronary arteriosclerosis is absent or is only minimal. Coronary insufficiency without coronary thrombosis but with myocardial infarction has been reported following shock due to pulmonary embolism,[2h] calcific aortic stenosis,[21] surgical operations, hemorrhage from ulcerative colitis and from duodenal ulcer,[2j] heart failure and infections. The myocardial lesions in coronary insufficiency are localized mainly in the subendocardial region, which is the portion of the myocardium farthest removed from the blood supply and, therefore, the part most severely affected by a relative inadequacy of the coronary blood flow. The characteristic alteration of the electrocardiogram, namely, a depression of the RS-T segment, has been attributed to the subendocardial localization of the infarction.

SUMMARY AND CONCLUSIONS

A series of 18 proved cases of coronary thrombosis or insufficiency following shock of varied origin has been presented. Arteriosclerosis of the coronary arteries is a major factor predisposing to coronary thrombosis and insufficiency in the presence of shock. The duration of the shock episode influenced the incidence of coronary thrombosis. A history of shock lasting one hour or longer was present in a majority of the patients in this series. On the other hand, the length of survival after shock affected the likelihood of the subsequent development of myocardial infarction. In the present series of patients, when the period of survival was less than 12 hours myocardial infarction was not observed.

The practical conclusion which can be drawn from this study is that patients in whom arteriosclerosis of the coronary arteries is probably present, that is, those whose ages are 50 years or more, are particularly susceptible to coronary thrombosis and insufficiency as a result of shock. Any fall in blood pressure, whether due to hemorrhage, trauma, spinal anesthesia or other causes, should be prevented; if a fall does occur, it should be treated as soon as possible. It is particularly important that the period of shock should not be permitted to exceed more than a few minutes. In the present series of patients the amounts of blood and plasma administered were usually insufficient. The transfusion of adequate quantities of blood or plasma by increasing the output of blood from the left ventricle and augmenting the coronary blood flow should significantly reduce the tendency to coronary thrombosis and insufficiency in shock.

4. Paterson, J. C.: Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis, Arch. Path. **25**:474-487 (April) 1938.

METASTATIC VERSUS PRIMARY CARCINOMA OF THE RECTUM

HARRY E. BACON, M.D.
AND
JOHN LAURENS, M.D.
PHILADELPHIA

IT IS a well established fact that metastatic tumors arising in distant sites may encroach on the rectum, producing symptoms referable to the lower part of the bowel and findings misinterpreted as those of a primary rectal malignant growth. It is the purpose of this paper to report an unusual case of a carcinoma of the breast which metastasized to the rectum, producing a diffuse infiltrative lesion which was thought to be a second primary growth arising in the rectum.

Involvement of the rectum by metastatic growths from extrapelvic organs is not uncommon. Malignant or nonmalignant processes, in the immediate vicinity of the rectovesical or rectouterine sulcus, may easily assume the form of an extension or shelf by impinging on the anterior rectal wall. The differential diagnosis of such processes is usually not difficult if one is familiar with the anatomy of the pelvic organs in the male and the female. However, secondary involvement of the rectum by neoplasms arising in the breast or the upper abdominal organs deserves more than cursory mention. The earliest reference to the entity is that by Strauss [1] in 1895, who reported a case of gastric carcinoma with metastasis to the pouch of Douglas. Four years later he cited two additional cases and mentioned that such metastasis may not only be early but may be the only manifestation. In 1908 Schnitzler [2] described 11 cases, in one of which the pancreas was the primary site. He stated: "The important feature was, that all these patients consulted the doctor for symptoms produced by the metastasis without having the slightest suspicion of the presence of the primary growth." Others have reported similar cases and Blumer,[3] in 1909, reviewed the literature in addition to reporting two cases, one primary in the gallbladder and the other in the stomach. Because of his excellent description, this extrarectal site has been referred to frequently as "Blumer's shelf."

Dr. Laurens is a resident in the Department of Proctology, Temple University Hospital and Medical School.

1. Strauss, H.: Über die Abhängigkeit der Milchsäuregährung vom HCl Gehalt des Magensaftes, Ztchr. klin. Med. **28**:584, 1895.

2. Schnitzler, J.: Über eine typische lokalisierte Metastase des Magenkarcinom, Med. u. Chir. **19**:205, 1908.

3. Blumer, G.: The Rectal Shelf: A Neglected Rectal Sign of Value in the Diagnosis and Prognosis of Obscure Malignant and Inflammatory Disease Within the Abdomen, Albany M. Ann. **30**:36, 1909.

The stomach has been found to be by far the commonest site affected. Feldner states that metastasis to the cul-de-sac occurs in 20 per cent of gastric carcinomas and in 18 per cent of those arising in the gallbladder. The explanation for the occurrence of carcinomatous implants in the abdomen, first mentioned by Schnitzler,[2] is almost universally accepted, namely, that pelvic involvement from a malignant process of the stomach or gallbladder occurs from fragments of cancerous tissue gravitating to the cul-de-sac. Eusterman and Balfour [4] are of the opinion that when the tumor reaches the gastric serosal layer carcinoma cells are mechanically carried to the pelvis and there occasionally take root. However, this does not explain entirely the occurrence of an isolated metastatic pelvic deposit in the absence of other visible and palpable implants. In two instances, sections of the smaller retroperitoneal lymphatic vessels in the lower dorsal and lumbar regions presented evidence of malignant invasion. Some investigators contend that lymphatic embolism and continuous permeation are commonly associated. Ewing [5] feels that the rapidly growing epidermoid and glandular carcinomas disseminate chiefly by lymphatic embolism, while the slowly growing and recurrent tumors often extend by continuous permeation. Retrograde flow through lymphatic and blood channels likewise has been a topic of much discussion. Organs in which there is a normal venous pulse or in which there occurs violent expiration or increase of intrathoracic pressure would be those most commonly involved. Occlusion of the main lymphatic or venous channels may give rise to disordered function as a result of which retrograde flow, even though a slow process, may supervene.

Walther [6] believes that many of the cases with alleged retrograde lymph node metastasis are instances of continuous dissemination because, in the majority of his cases, he demonstrated that diseased lymph nodes not in the vicinity of the primary growth were regional metastases of an organ that had become involved by the hematogenous route.

The occurrence of widespread metastases in carcinoma of the breast is not infrequent. Abrams, Spiro and Goldstein,[7] in a postmortem analysis of 1,000 consecutive cases of malignant neoplasms of epithelial orgin to determine the incidence of metastases, found 167 carcinomas of the breast in every one of which metastasis had occurred. Involvement of multiple organs was frequent, and in more than 60 per cent of the cases five organs were involved. There were 24 instances in which the gastrointestinal tract was the site of metastasis, the majority of these being serosal. Ewing [8] states that mammary cancer, after reaching the axillary nodes and

4. Eusterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, p. 103.

5. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 412.

6. Walther, H. E.: Investigations in Cancer Metastasis, Ztschr. Krebsforsch. **46**:313, 1937.

7. Abrams, H. L.; Spiro, R., and Goldstein, N.: Metastases in Carcinoma: Analysis of 1000 Autopsied Cases, Cancer **3**:74, 1950.

8. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 584. Feldner, cited by Yeomans, F. C.: Proctology: A Treatise on the Malformations, Injuries and Disease of the Rectum, Anus and Pelvic Colon, ed. 2, New York, D. Appleton-Century Company, 1936, p. 505.

the muscular aponeuroses, usually becomes generalized and nearly any tissue in the body may become involved. Freid and Goldberg,[9] in a study of 131 autopsies in cases of cancer of the breast, found metastasis to the gastrointestinal tract in 14, the stomach in seven, the intestines in four and the gallbladder in three. Saphir and Parker [10] reviewed 43 necropsies and found similar involvement in six, with the gastrointestinal tract involved in three, the gallbladder in two and the intestinal wall in one. Warren and Witham [11] reported 162 cases, with peritoneal metastasis in 21 but no mention of the gastrointestinal tract per se. In none of the above-mentioned series, however, was there a case in which the rectum itself was involved.

The mode of spread of cancer of the breast has been carefully investigated by numerous workers. Gerota,[12] with reference to recurrent mammary carcinoma and invasion of epigastric and inguinal nodes, injected the lymphatic vessels from the breast along the superior and inferior epigastric arteries to the inguinal nodes. He assumed that the recurrent tumor had widened those vessels by disturbing the normal lymph flow. Stiles [13] points out that the xiphoid process is only 2.5 cm. from the inferior border of the breast, which is less than the distance to the mediastinal nodes and that, in this location, only a thin fibrous area rich in lymphatic vessels separates the mammary fat from the subperitoneal adipose tissue and the suspensory ligament of the liver. Handley [14] emphasizes the importance of extensions along the muscular aponeuroses. He was able to show that mammary cancer travels by continuous permeation, chiefly in the vessels of the muscular aponeuroses and extends not only over the pectoralis but over the serratus magnus, obliquus and rectus muscles, below the xiphoid process and across the median line, covering an oval area 25 cm. in diameter. He concludes that invasion of the peritoneum from the epigastric aponeuroses, by way of the parietes or the falciform ligament of the liver, occurs in at least 44 per cent of instances. In 422 autopsies the abdominal organs were involved, and the lungs were free in 53, indicating that the abdominal extensions did not pass through the thorax. Handley maintains that in nearly every case of breast carcinoma dissemination in the abdominal cavity occurs by transcelomic spread, the secondary deposits arising from gravitation of cancerous particles into the pelvis, and that in the late stage the entire pelvis may be filled with cancer. "It must never be forgotten, that the first sign of epigastric invasion may be found, not in the epigastric region, but in the pelvis." [15]

During the five year period from 1933 to 1938, one of us [16] observed 22 cases of a malignant process of the upper abdominal and mammary regions with meta-

9. Freid, J. R., and Goldberg, H.: Frequency, Clinical Course and Treatment of Metastases from Cancer of the Breast, Am. J. Roentgenol. **50**:499, 1943.

10. Saphir, O., and Parker, M. L.: Metastasis of Primary Carcinoma of the Breast, with Special Reference to Spleen, Adrenal Glands and Ovaries, Arch. Surg. **42**:1003 (June) 1941.

11. Warren, S., and Witham, E. M.: Studies on Tumor Metastasis: The Distribution of Metastases in Cancer of the Breast, Surg., Gynec. & Obst. **57**:81, 1933.

12. Gerota, cited by Ewing,[5] p. 585.

13. Stiles, cited by Ewing,[5] p. 585.

14. Handley, W. S., cited by Ewing.[5]

15. Handley, W. S.: Cancer of the Breast, ed. 2, New York, Paul B. Hoeber, Inc., 1922, p. 234.

16. Bacon, H. E.: Extrarectal Metastatic Malignancy Simulating Primary Carcinoma of the Rectum, New York J. Med. **39**:2267, 1939.

static involvement of the pelvic sulcus (see table). During the 15 year period ending September 1948, a total of 46 cases was seen, the growth in two of these being primary in the breast.[17]

A perusal of the table reveals that in the majority of instances symptoms referable to the lower part of the bowel were cited by the patient, although not those symptoms so frequently stated that are suggestive of primary carcinoma of the rectum, viz., change in bowel habit, early morning diarrhea, frequency, urgent desire for and incompleteness of stool, and bleeding.

We should like to report a case of a carcinoma of the breast with metastasis to the rectum producing symptoms referable to the lower part of the bowel, together with physical findings and pathological features compatible with a primary carcinoma of the rectum.

REPORT OF A CASE

A 72 year old white woman was admitted to our service at Temple University Hospital on Feb. 3, 1949, with a chief complaint of "tightness of the anus" and "a mass on the right side of the rectum." She stated that she had had intermittent diarrhea during the early years of her life. For the past 10 years she had suffered from chronic constipation. During the past few months her constipation had progressed, until her stools had become "pencil-like." For the

Distribution of Carcinoma in Forty-Six Cases

Primary Site	No. of Cases
Stomach	21
Pancreas	5
Ascending colon	4
Breast	2
Common bile duct	1
Esophagus	1
Kidney	1
Retroperitoneum	1
Total	46

past two months she had noted bright blood with her bowel movements, which were occasionally accompanied with pain. Just prior to her admission she had complained of a bearing-down feeling and a sensation of pressure in the rectum. There had been no weight loss. She was seen by her physician, who found a "stricture of the rectum" and referred her for further treatment.

The past history revealed that in 1940 the patient had undergone a simple mastectomy for carcinoma of the left breast. In July 1948 a palliative, radical mastectomy and axillary node dissection were performed at Johns Hopkins Hospital by Dr. Mark Ravitch, inoperable supraclavicular and axillary metastases being present.

On physical examination, the blood pressure was 150 systolic and 80 diastolic; the weight was 137 pounds (62 Kg.), and the height 60 inches (152 cm.). Inspection of the chest revealed absence of the left breast, with a long scar extending into the axilla, where a hard fixed mass was felt. The heart and lungs were entirely normal. Examination of the abdomen was noncontributory, except for a questionable mass in the left inguinal region below Poupart's ligament. The pelvic findings were as follows: The external genitalia were atrophic, the entire rectovaginal septum was indurated and tender from the introitus to the apex of the vagina, the induration being smooth and firm with no palpable nodules, the cervix was atrophic and clean, the corpus appeared to be about normal in size and freely movable and no adnexal disease was outlined.

Examination of the rectum revealed external hemorrhoids of the varicose variety. On digital examination, considerable scarring was felt in the anal canal, with stenosis of the

17. Bacon, H. E.: Anus, Rectum, Sigmoid Colon (Diagnosis and Treatment), ed. 3, Philadelphia, J. B. Lippincott Company, 1949, p. 678.

lower part of the rectum. On proctosigmoidoscopy, there were no abnormalities except for the strictured area low in the rectum, from which a biopsy specimen was taken. Cystoscopy revealed moderate elevation of the trigone, with several blebs on the mucosal surface.

Laboratory studies, including a complete blood count, urinalysis, serologic tests, serum protein, chloride and blood urea nitrogen determinations and liver function tests, gave values which were all within normal limits. Roentgenograms of the chest showed a healed fracture of

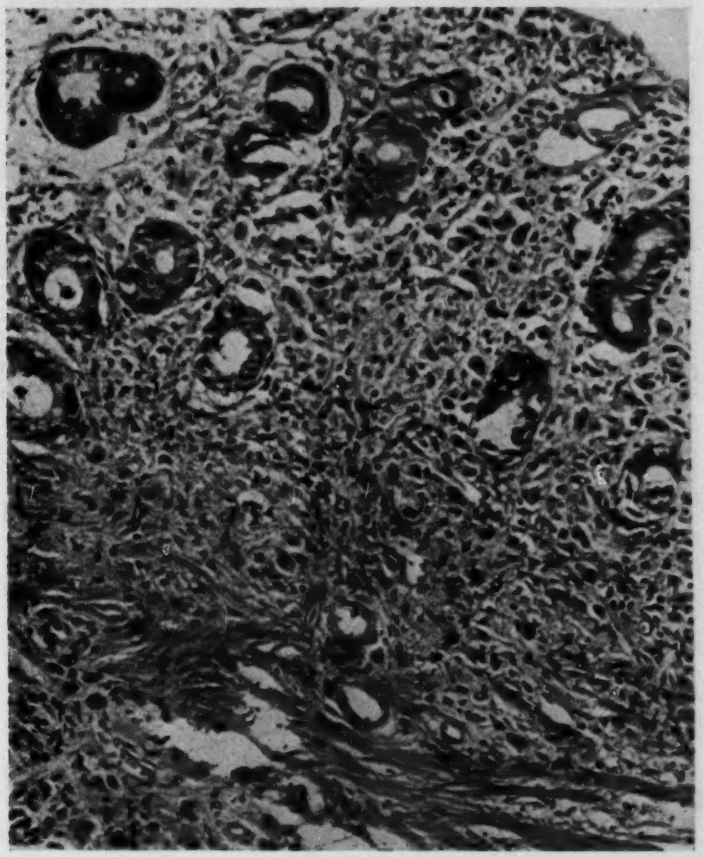


Fig. 1.—Microscopic view of rectal specimen, showing intact, relatively normal glands and an infiltration of the mucosa and submucosa by cords of large cells with hyperchromatic nuclei and pale cytoplasm. These cells also appear singly. They do not appear to be arising from the glands. A sprinkling of lymphocytes is also seen.

the left seventh rib, with no parenchymal diseases. There was no evidence of any skeletal metastasis. Barium enema and air contrast studies of the colon showed it to be normal. The electrocardiogram was within normal limits.

The pathologic report on the rectal biopsy was "diffuse infiltrative carcinoma of the rectum" (fig. 1).

On Feb. 22, 1949, an abdominoperineal proctosigmoidectomy was performed. Exploration of the abdomen revealed no gross metastasis in the liver or peritoneum, and there was no glandular involvement. However, there was extension of the process, which may have been inflammatory, into the anterior sacral space and under the peritoneum, laterally on each side as well as to the posterior vaginal wall. This was particularly evident in the perineal phase.

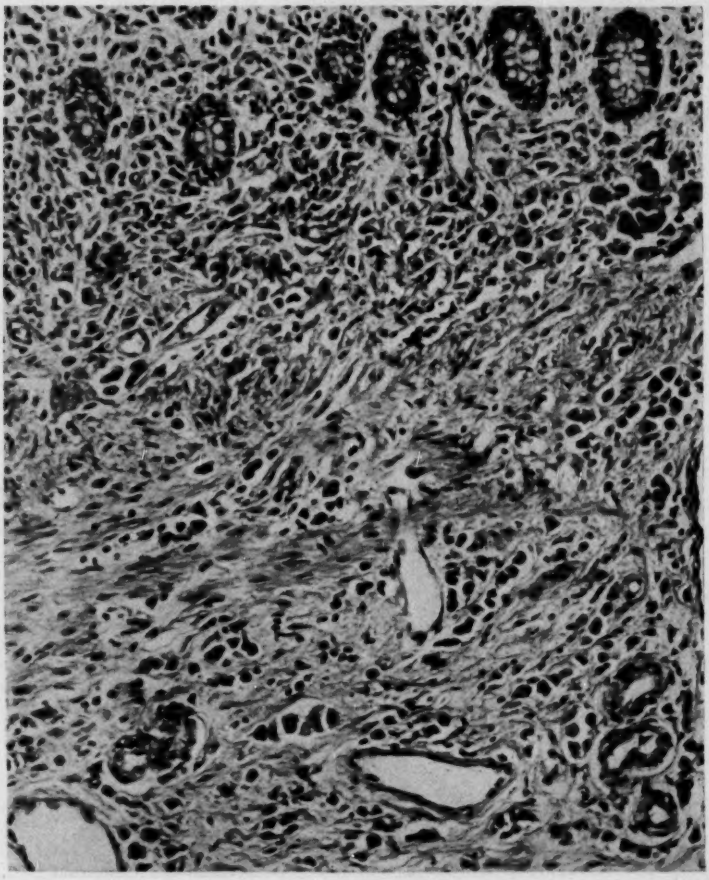


Fig. 2.—Section through the removed bowel tumor, which shows a similar picture to that of figure 1. Dilated, thin-walled, endothelium-lined spaces are prominent, some of which contain tumor cells in their lumens. These spaces probably represent lymphatic channels. Again the glands have a relatively normal appearance. The tumor cells penetrated the entire thickness of the wall.

Postoperatively, the patient had a rather stormy course marred by acute pyelonephritis with a nonfunctioning left kidney. However, this responded satisfactorily, and she was discharged on April 10, 1949.

The gross pathologic report first rendered was as follows: "The specimen consists of approximately 22 cm. of rectum and 4.5 cm. of anal canal. The six most distal centimeters of

rectum have a thickened wall measuring 1 cm. in diameter and a mucosal surface which is intact but reddened and nodular. Numerous enlarged lymph nodes are found in the attached fatty tissues." The microscopic report was as follows: "Sections reveal the entire wall as well as the perirectal tissues to be infiltrated by diffuse nests and sheets of large hyperchromatic neoplastic cellular elements. There is a considerable desmoplastic reaction. The regional lymph

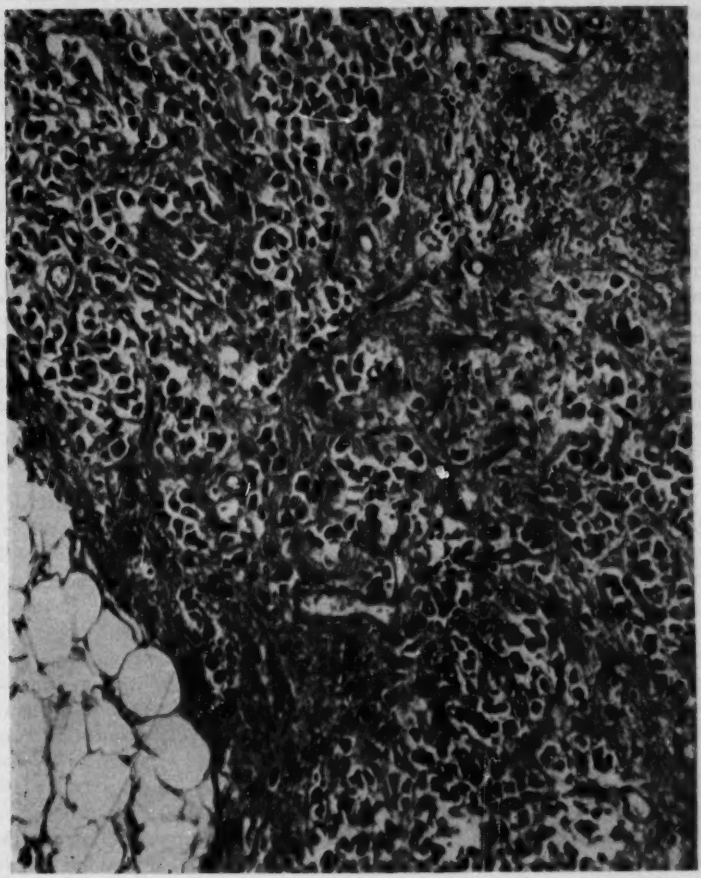


Fig. 3.—Microscopic view of the breast carcinoma. Embedded in a fibrofatty background there are nests and cords of tumor cells similar to those described in figures 1 and 2, thus justifying our conclusions that the rectal wall tumor represents a metastasis from the breast.

nodes show diffuse metastatic tumor involvement. The diagnosis was infiltrative carcinoma of the rectum, grade 4, with lymph node metastasis."

Because of the past history, the physical findings and the character of the malignant cells, slides on the breast lesion were obtained from Johns Hopkins Hospital (courtesy of Dr. Mark Ravitch) and a review of the case was requested. After a careful study of all the sections, a

supplementary report was submitted by Dr. A. R. Peale, Department of Pathology, Temple University Medical School, as follows:

"A review of the slides on this case was requested because of the history of a breast carcinoma removed eight years ago and again one year ago for recurrence. The problem as to whether the bowel lesion represents a metastasis from the breast or a second unrelated malignant process has arisen. This is a difficult decision to make on cystologic grounds since malignant tumors from both sites are usually epithelial and since their morphology may be similar, particularly in their anaplastic forms. Admittedly, diffuse infiltrative carcinoma of the large bowel is relatively uncommon, although we have seen one such lesion recently. The morphology of the bowel lesion is striking, in that the cells are large and polyhedral and are reminiscent of neoplastic duct cells from the breast. I am in favor of the notion that the bowel lesion represents a metastatic form from the breast, probably by retrograde lymphatic spread, although I am willing to admit that this is a personal interpretation and the possibility of a double primary growth in the breast and in the bowel cannot be eliminated. The diagnosis is diffuse infiltrative carcinoma of the rectum, probably metastatic from the breast (fig. 2).

"The outside slides, submitted from the breast, show a diffusely infiltrative anaplastic carcinoma similar in its morphology to the lesion seen in the bowel. The diagnosis is undifferentiated carcinoma of the breast with bowel metastasis" (fig. 3).

The patient returned to Temple University Hospital on April 16, 1950, with a chief complaint of diarrheas of two weeks' duration. About six months previously, she had had a course of high voltage x-ray therapy to the pelvis. She had also received some hormonal therapy. Examination at this time revealed marked pallor and dehydration. There was a large fixed mass in the left axilla. The liver was palpable three fingerbreadths below the right costal margin and was nodular. Hard fixed nodes were felt in the left inguinal region, and on vaginal examination the pelvic structures were frozen. Laboratory studies revealed secondary anemia and mild acidosis. She was treated for this and discharged on April 20, 1950.

COMMENT

The problem as to whether the lesion in this case was secondary or primary is interesting. Long and others [18] studied 30 operative specimens from the large intestine and rectum which had been excised for carcinoma of these regions. The study was limited to cases in which a primary carcinoma had been removed at the Mayo Clinic at least one year before the patient returned with another lesion in the same region, which was considered to be a recurrent carcinoma by all concerned. Cases in which the second growth appeared in remote segments of the colon were discarded. These authors undertook to determine whether patients with evidence of a carcinoma of the colon or rectum in the region of a previously removed lesion had a recurrence of the carcinoma or a new and independent neoplasm. Dockerty [19] has shown that carcinomas of the colon extended by progressive conversion of the surrounding adjacent mucosa into tumor. This theory was first advanced by Thiersch [20] in 1865 and is adhered to by most modern pathologists. As brought out by the study of Long,[18] if the aforementioned concept is true, there should be a transition zone between the carcinoma and the surrounding adjacent mucosa. These investigators clearly demonstrated this zone in nine of the 30 cases and used it as an additional criterion with which to prove the authenticity of multiple primary carcinomas of the colon.

18. Long, J. W.; Mayo, C. W.; Dockerty, M. B., and Judd, E. S.: Recurrent Versus New and Independent Carcinomas of the Colon and Rectum, Proc. Staff Meet., Mayo Clin. **25**:169, 1950.

19. Dockerty, M. B., cited by Long.[18]

20. Thiersch, cited by Willis, R. A.: Pathology of Tumors, St. Louis, C. V. Mosby Company, 1948, p. 106.

With regard to multiple primary carcinomas, most authors use the criteria established by Warren and Gates,[21] as follows: 1. Each tumor must present a definite picture of a malignant process. 2. Each tumor must be distinct. 3. The probability of one being a metastasis of the other must be ruled out. Bacon and Tavenner,[22] in a review of multiple primary malignant growths involving the colon

Fig. 4.—Section of a primary adenocarcinoma of the bowel, taken at the edge of the tumor, to show a transition zone between the normal and the frankly neoplastic glands.

and rectum, found 7.3 per cent which satisfied these criteria. Of the total series of 85 cases, there were four with primary carcinomas of the breast and colon or rectum.

21. Warren, S., and Gates, O.: Multiple Primary Malignant Tumors: A Survey of the Literature and a Statistical Study, Am. J. Cancer **16**:1358, 1932.

22. Bacon, H. E., and Tavenner, M. D.: Multiple Primary Malignancy Involving the Colon and Rectum, Am. J. Surg., to be published.

With these points in mind, we again reviewed figures 1 and 2, which are microscopic sections, respectively, of the rectal biopsy and the final specimen removed in the case which is the subject of this paper. In both sections infiltrating neoplastic cells may be seen in the wall of the bowel beneath a mucosa that appears normal. The glands are regularly arranged and the nuclei normally stained and lined up along the basement membrane. However, in figure 4, a section taken from a primary adenocarcinoma of the rectum, the histopathologic pattern is different. Here is disclosed a gradual transition from normal glands to glands which are irregularly arranged and whose nuclei are deeply stained and have migrated away from the basement membrane and finally to glands which are frankly malignant.

From this study we can conclude that the case reported is an example of metastasis of a primary carcinoma of the breast to the rectum, producing symptoms and findings which led us to believe that we were dealing with a new and independent carcinoma of the bowel. It is hoped that this discussion will increase our understanding of the problem of metastatic versus primary carcinoma of the rectum.

SUMMARY

An unusual case of a metastatic carcinoma of the breast involving the rectal wall is reported. Metastatic tumors arising in distant sites may encroach on the rectum, producing symptoms referable to the lower part of the bowel and findings misinterpreted as those of primary rectal carcinoma.

From 1933 to 1948, 46 additional cases of malignant growths of the upper abdominal and mammary regions with metastatic involvement of the pelvic sulcus were observed. A discussion of the mode of spread in such cases is presented, with particular reference to the breast.

The microscopic picture of metastatic and primary carcinomas of the rectum is reviewed, with special emphasis on the transition zone between the carcinoma and the surrounding adjacent mucosa.

TOTAL PAROTIDECTOMY IN TUMORS OF THE PAROTID GLAND

WILLIAM S. McCUNE, M.D.
WASHINGTON, D. C.

THE PAROTID, like other salivary glands, is the site of origin of a variety of tumors. Such lesions, though of various types, benign and malignant, are for the most part rare, with the exception of mixed tumors and carcinomas. The latter are the subject of this discussion.

Since the first description of mixed tumors of the parotid by Virchow [1] in 1863 the origin and classification of salivary gland tumors, both benign and malignant, has been disputed by pathologists throughout the world. Because of the presence of cartilage in some tumors, Virchow spoke of them as "diffuse enchondromas" and thought them to be of mesoblastic origin. With the finding of epithelial elements, however, the composite nature of the tumors became evident to him, and he first used the term "Zusammengesetze Geschwülste" or mixed tumors. In 1877, Cohnheim [2] suggested that in an early stage of embryonic development more cells are produced than are required and a number of unappropriated cells remain, which, because of their embryonic character, have a great capacity for growth. Cohnheim believed that mixed tumors arise from these cells, a theory which is held by many pathologists today. In 1879, Wartmann [3] expressed the belief that the polyhedral and epithelium-like cells of these tumors are of endothelial origin. Krompecher [4] in 1908 thought them to originate from the basal layer of stratified epithelium and called the tumors "basaliomas." In 1906 Ehrich [5] noted mucoid degeneration of epithelial cells in salivary gland tumors, with later transformation into cartilage. This theory of origin of the mucoid tissue and cartilage is now widely accepted.

Histologically, mixed tumors consist primarily of parenchymatous and interstitial tissues. The parenchyma may be scanty or abundant. It may contain structures resembling acini and ducts but never resembling them so closely as to be mistaken for a normal gland. The interstitial tissue varies from soft mucilaginous substance to dense cartilage-like material containing poorly defined masses of bone.

From the Department of Surgery, The George Washington University School of Medicine and Walter Reed Army Hospital.

1. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, vol. 1, p. 502.

2. Cohnheim, J.: Vorlesungen über allgemeine Pathologie, Berlin, A. Hirshwald, 1882, vol. 2, p. 736. Cohnheim, J., cited by McFarland, J.: Mysterious Mixed Tumors of Salivary Glands, Surg., Gynec. & Obst. **76**:23-34 (Jan.) 1943.

3. Wartmann, A. H.: Inaugural Dissertation, Strassburg, 1880.

4. Krompecher, E.: Zur Histogenese und Morphologie der Mischgeschwülste der Haut sowie der Speichel- und Schleimdrüsen, Beitr. path. Anat. **44**:51-87, 1908.

5. Ehrich, E.: Zur Kenntnis der Speicheldrüsentumoren: histologische und klinische Untersuchungen, Beitr. klin. Chir. **51**:368-496, 1906.

Mixed tumors, although commonest in the parotid gland, are rare. Of 413 salivary gland tumors collected by McFarland,[6] there were 389 parotid, 12 submaxillary and 12 sublingual tumors. Over a 25 year period McFarland found that 24 Philadelphia hospitals averaged only 15 operations a year for such tumors. Two hundred and thirty-three patients over the 25 year period were operated on by 73 surgeons, an average of 3.2 each.

The question of whether or not mixed tumors are malignant has never been thoroughly settled. Ewing[7] suggested the following clinical criteria of malignancy: (1) infiltrative growth, (2) local destructive properties, (3) recurrence after removal, (4) formation of metastases, (5) local interference with function and (6) general toxic action of absorbed tumor products.

1. Mixed tumors are usually well encapsulated and therefore rarely infiltrate. Tumor cells, however, are often scattered in islands among the fibrous layers of the capsule so that if the latter is opened through traumatic accident or surgical intervention, infiltrative growth may take place. In one case reported by McFarland, after two operations for primary and recurrent resection a tumor invaded the orbit

Fig. 1.—Large mixed tumor of the parotid gland of many years' duration without nerve paralysis or ulceration of the skin.

causing exophthalmos, eventually penetrating the cranial cavity and bringing about death by compressing the brain. Such cases are rare.

2. Mixed tumors usually project externally so that the skin is the organ most affected. The skin and other structures of the face stretch so easily, however, and these tumors grow so slowly that even huge growths (fig. 1) may not cause local tissue damage. If injured, the skin sometimes becomes ulcerated, and even fatal hemorrhage may occur.

3. Recurrence is the most inaccurately reported of all complications of mixed tumors. This inaccuracy depends on the failure of surgeons to follow cases for a long enough time. Most recurrences do not appear until three to seven years after operation, and many do not appear for 20 or 25 years. The longer any series of cases is followed the higher the rate of recurrence. Of 400 cases studied by

6. McFarland, J.: Mysterious Mixed Tumors of Salivary Glands, Surg., Gynec. & Obst. **76**:23-34 (Jan.) 1943.

7. Ewing, J.: Neoplastic Disease: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

McFarland, recurrences are known to have occurred in about 100. Recurrence rates of other authors are summarized in table 1.

TABLE 1.—*Recurrence Rates of Parotid Tumors*

	Marshall and Miles*	McFarland§	Janes†	Sistrunk‡	Benedict and Meigs‖	Stein and Geschickter¶
Benign parotid tumors	15%	34.2%	0	18.3%	42.5%	20%
Recurrent benign parotid tumors	50%	.....	.....	37.8%	.....	....
Carcinoma of parotid gland	90%	100%	66⅔% (3 yr.)	.....	.....	....
Recurrent carcinoma of parotid gland	100%	.....	.....	.....	.....	....

* S. Clin. North America 27:501 (June) 1947.
† S. Clin. North America 23:1429 (Oct.) 1943.
‡ S. Clin. North America 1:1515 (Oct.) 1921.
‖ Surg., Gynec. & Obst. 51:626 (Nov.) 1930.
¶ Arch. Surg. 28:492 (March) 1934.

Two theories have been suggested for the great tendency of mixed tumors to recur. One is that through trauma to the lesion during removal bits of the tumor are left behind to recur. The presence of neoplastic cells in the capsule itself lends support to this theory, for in efforts to avoid injury to the facial nerve,

Fig. 2.—Large, apparently encapsulated adenocarcinoma of the parotid gland in a 73 year old man. After removal the patient lived for 3½ years without recurrence, after which he died of heart disease.

it is inevitable that at times bits of the capsule must be left behind. These fragments of capsule may contain tumor cells. The second theory is suggested by Cohnheim's belief that mixed tumors originate from rests of embryonic cells which begin to proliferate later in life. Obviously, removal of one encapsulated tumor does not preclude the presence of other embryonic cells elsewhere in the parotid, which begin to multiply years later, producing a "recurrent" tumor.

4. Although occasional instances of metastasis of mixed tumors to regional glands have been reported, they are so rare that for all practical purposes the tumors can be regarded as nonmetastasizing.

5. and 6. Mixed tumors occasionally interfere with opening and closing of the mouth, and may block the external auditory canal or distort the lower lid of the eye. In general, however, the lack of interference with normal function is more remarkable than its occurrence. Absorption of toxic products from these tumors has never been reported.

Mixed tumors therefore may be regarded as benign lesions with a strong tendency toward recurrence. Whether or not they ever undergo malignant transformation is not entirely clear, although it seems probable that they do not. This question is confused by frequent instances of parotid carcinomas which lie in a

dormant state for many years and then suddenly begin to show signs of rapid growth and invasion of surrounding structures and to metastasize (fig. 2). Furthermore, as pointed out by McFarland, if we are to admit that benign mixed tumors sometimes become malignant, we must also consider that perhaps malignant parotid tumors "become benign." Certainly there are many lesions almost indistinguishable from carcinomas histologically which never invade, metastasize or show any other characteristics of a malignant process except a strong tendency to recur. These McFarland called "carcinomatoids," distinguishing them clinically from carcinomas by their longer preoperative duration, slower rate of growth and absence of metastases.

CLINICAL MANIFESTATIONS AND TREATMENT

Mixed tumors of the parotid gland begin as small, firm, nodular, movable growths causing no symptoms (fig. 3). They may occur in any part of the gland, though most frequently they are directly anterior to the external auditory canal. Several tumors in this series presented themselves as small lumps just posterior

Fig. 3.—Mixed tumor of the parotid of 12 years' duration.

to the angle of the mandible, but a large part of the tumors extended upward behind the mandible to the floor of the skull. They may grow slowly for as long as 30 years without invading surrounding structures or metastasizing. The overlying skin stretches readily with the slow growth of the tumor, and although it may eventually become ulcerated if stretched too tightly, this rarely occurs. The seventh nerve also withstands a surprising degree of pressure from large tumors, and it is not uncommon to see very large growths without evidence of facial nerve paralysis. Cotterhill [8] described a tumor weighing 22 pounds (10 Kg.) without ulceration or facial nerve paralysis. Eventually, however, both the fifth and the seventh nerve may become involved.

Carcinoma of the parotid gland differs from mixed tumors in most important respects. Although growth may be slow it is usually much more rapid than in benign tumors. Infiltration occurs early in most cases although occasionally the tumor may remain completely encapsulated for a time. As infiltration occurs, branches of the seventh and fifth nerves become involved, with facial paralysis and

8. Cotterhill, cited by McFarland.[6]

pain before the tumor has reached any large size. The mandible may be involved early, producing pain on mastication and limitation of action of the temporomandibular joint. The tumor itself is firm, fixed and may or may not be slightly tender. Metastasis may occur through lymphatic vessels to regional lymph nodes, or through the blood stream to the lungs and to other organs throughout the body. According to Houck,[9] 20 per cent of cases of large, malignant tumors of the salivary glands present lymph node metastases in the neck, but distant metastases are almost never present at the stage in which the patient presents himself for treatment.

Surgical removal has always been regarded as the treatment of choice in mixed tumors of the parotid gland. Although radiation therapy has been used, including the implantation of radon into the tumor capsule, response to radiation is poor and damage to the facial nerve may result from too vigorous dosages. Prior to the work of Sistrunk in 1921, surgical treatment consisted in exposure of the tumor and its removal with preservation of the branches of the seventh nerve as they were encountered. In 1921 Sistrunk pointed out that mixed tumors of the parotid gland recur 10 or 11 times more frequently than similar tumors of the submaxillary gland. He recommended isolation of the inframandibular branch of the facial nerve, tracing it back to the bifurcation of the nerve trunk itself, and dissection of all its branches before removal of the tumor. In 1923 Adson and Ott [10] supported this method in all but simple cases and also advised removal of the entire parotid gland through a Y-shaped incision beginning anterior and posterior to the external ear. In 1941 Bailey [11] pointed out that the parotid gland is composed of a large superficial lobe and a smaller deep lobe. He recommended the performance of complete parotidectomy by first removing the superficial lobe and then picking up the main trunk of the facial nerve and using the superior border of the digastric muscle as a guide. He then advised dissection of all branches of the nerve and finally removal of the deep lobe of the gland. He recommended ligation of the external carotid artery in many cases.

Treatment in carcinoma of the parotid gland has consisted in various forms of radiation, surgical intervention or both, but regardless of the methods employed the results have been discouraging. Benedict and Meigs in 1940 recommended radical surgical extirpation with or without radiation but stated that patients rarely lived for longer than two years after operation. Of 30 patients with proved carcinoma of the parotid gland only one survived, making an ultimate mortality of 96.7 per cent. Of nine patients with sarcoma of the parotid, three lived for more than five years but only two failed to die of sarcoma. In 1939 Houck stated that the average life expectancy after operation is two years, and he felt that operative trauma tends to accelerate growth. He summarized the findings of other workers, including Ahlborn.[12] At Radiumhemmet in Stockholm, Ahlborn recommended radiation therapy in practically all cases at an early stage followed by operation in cases of radiosensitivity. He reported 23 per cent of 62 patients to be free

9. Houck, J. W.: Tumors of Salivary Glands: Review of Prognostic Data from Literature, Surgery **6**:550-564 (Oct.) 1939.

10. Adson, A. W., and Ott, W. O.: Preservation of the Facial Nerve in Radical Treatment of Parotid Tumors, Arch. Surg. **6**:739-746 (May) 1923.

11. Bailey, H.: Treatment of Tumours of Parotid Gland, with Special Reference to Total Parotidectomy, Brit. J. Surg. **28**:337-346 (Jan.) 1941.

12. Ahlborn, H. E., cited by Houck.[9]

from symptoms and signs after five years on radiation therapy alone and 40 per cent of 35 patients free from symptoms and signs for five years after surgical treatment and radiation. In 1942 McFarland reported 100 per cent recurrence of carcinoma after excision. Marshall and Miles in 1947 found a 90 per cent five year recurrence rate after surgical and/or radiation treatment of carcinoma of the parotid gland and a rate of 100 per cent in cases of recurrent carcinoma.

The common complications of operations for parotid tumors are recurrence, facial nerve paralysis and, more rarely, salivary fistula. McFarland found that most recurrences occur at about seven years but that they may come as late as 40 or 45 years after operation. Marshall and Miles stated that although most recurrences appear within five to seven years, 85 per cent are evident within three years. Bailey cited R. Kennon as revealing that although recurrence can take place after many years it usually appears within 12 months. Facial nerve paralysis should be expected after radical excision of malignant parotid tumors, and division of individual fibers is occasionally necessary in large benign tumors, though these

TABLE 2.—*Paralysis of Facial Nerve*

	Total, %	Benign, %	Malignant, %
Benedict and Meigs	13.7	7.5	20
Stein and Geschickter	....	10	....
McFarland	4.4	....	....
Ahlborn	16.9	11	36.4
Marshall and Miles	14.5	10.6	30.4

	Mandibular Branch	
	Recurrent, %	No Previous Surgical Treatment, %
Lahey Clinic	16.6	5.4
	Complete	
Lahey Clinic	5.5	2.7

fibers should be resutured after removal of the tumor. Salivary fistulas are rare and almost never occur if the incision is closed without drainage. Results of other authors are given in table 2.

MATERIAL

Thirty-four patients were operated on at Walter Reed General Hospital for tumors of the parotid gland between 1942 and 1947. Except for a few older persons, all were of military age. In most instances the diagnosis of a parotid gland tumor had been made at an overseas installation, and in many cases a previous incomplete removal had been performed or a complete removal of the tumor, with later recurrence. In all instances in which a previous operation had been performed, pathological sections of the tissue removed were received. Frequently in mixed tumors the recurring lesion was more cellular and more rapidly growing than the original one. Twenty-seven of the 34 patients had mixed tumors, and seven had adenocarcinomas.

MIXED TUMORS

Twenty-seven mixed tumors of the parotid gland were operated on during the five year period. Twenty of the 27 have now been followed for more than five years. Surgical excision alone was used because although radiation may have had a slight effect occasionally on rapidly growing tumors in general it was ineffective

for these lesions. Five of the 27, or 18 per cent, were recurrent tumors. All mixed tumors were painless and nontender, and no patient had facial paralysis on his admission to this hospital. The tumors varied in diameter from 2 to 6 cm. and were situated in all parts of the parotid gland. Although the tumor in several

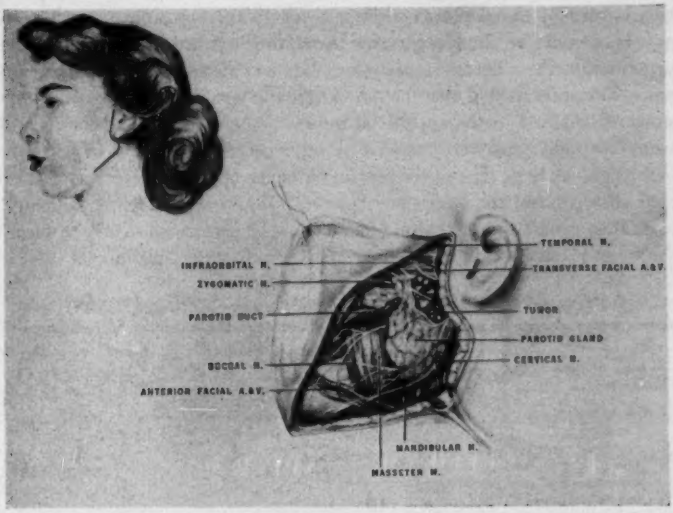


Fig. 4.—Dissection of parotid area as it appears in parotidectomy, showing mandibular division of facial nerve crossing anterior facial artery at anterior border of masseter muscle. Insert shows incision for total parotidectomy.

Fig. 5.—*A*, moderate-sized mixed tumor of parotid, showing typical forward displacement of external ear. *B*, incision seven days after total parotidectomy. *C*, same as *B*, anterior parotidectomy.

instances was only slightly visible posterolaterally to the mandible, it extended deeply into the pterygoid region to the floor of the skull.

The technique employed in all recurrent and in most of the primary lesions was total parotidectomy through a curved incision similar to that recommended

by Sistrunk. The scar in this location proved to be inconspicuous, and the exposure of the entire gland was satisfactory. General intratracheal anesthesia was used, the head turned strongly to the side opposite the tumor and the head of the table moderately elevated. The line of incision was marked before draping and skin towels sewed to the skin (figs. 4 and 5). After the incision was deepened the anterior border of the flap was dissected out sharply to a line just beyond the anterior border of the masseter muscle extending upward to the anterior end of the zygomatic arch. The posterior skin flap was dissected back to the mastoid process. The anterior flap must be thin where the terminal branches of the seventh nerve are distributed to the superficial muscles of expression and lie close to the surface. The skin flaps were handled by interrupted silk sutures to prevent damage to forceps. A large part of the remainder of the operation consisted in a careful, complete dissection of the entire facial nerve. When this had been accomplished, removal of the tumor and the parotid gland could be performed easily. In these cases the nerve was usually approached by first locating the mandibular division at

TABLE 3.—*Complications of Total Parotidectomy for Mixed Tumors*

	Primary	Recurrent	Total	Per Cent
Number of cases	22	5	27	..
Recurrences	2	0	2	8
Facial paralysis				
Complete	0	0	0	0
Complete (sacrificed)	0	1	1	4
Lower part of face	1	1	2	7
Lower part of face (sacrificed)	0	1	1	4
Degree unknown	1	..	1	4
Total number with facial paralysis	..	..	5	18.5
Salivary fistula	1	..	1	4

the point of intersection of the border of the mandible, the anterior maxillary artery and the anterior border of the masseter muscle. This branch was then traced back to the lower division of the nerve, and thence the entire nerve was dissected from the underlying tumor and gland, as recommended by Sistrunk. Great care was taken to avoid injury to the nerve, by keeping it moist with saline and handling it as little as possible with the use of rubber tissue strips only. The nerve was never picked up with forceps. Of great aid in identifying branches was the use of a peripheral nerve faradic stimulator. The effect of weak stimulation was observed by the anesthetist. No ill effects of such stimulation were noted in any cases. In some instances the nerve trunk was located at its exit from the stylomastoid foramen, as recommended by Bailey and James. Although this method is somewhat faster, damage to the nerve before it is recognized results in a more serious paralysis than damage to the mandibular branch alone. After dissection of the nerve the entire parotid gland was removed with the tumor after Stensen's duct was ligated and divided. Hemostasis must be meticulous, silk being used throughout the procedure. In large tumors ligation and division of the external carotid artery were occasionally performed at the beginning of the operation. The wound was closed without drainage and a pressure dressing maintained in position for four or five days.

The results of this procedure are shown in table 3. One salivary fistula persisted for two years but at last report had closed. There were no other salivary fistulas. Recurrence has been reported in only two cases, both involving primary tumors. There was one instance of complete facial paralysis following removal of a recurrent tumor, in which several branches were purposely sacrificed. There were four instances of paralysis of the mandibular branch only. In one of these the nerve was knowingly sacrificed because of the impossibility of removing the tumor completely without doing so. Two of the four involved recurrent tumors. In one case a branch of the nerve was divided and resutured to enable complete removal of the tumor, but paralysis of the branch persisted. There were only two instances of facial nerve paralysis following removal of a primary tumor, the remaining three occurring after the removal of recurrent tumors.

ADENOCARCINOMA

There were seven cases of adenocarcinoma of the parotid gland. All have been followed for five years. In spite of the clinical differences between mixed tumors and carcinomas noted above, the diagnosis of a malignant process was sometimes difficult. In such cases a biopsy with frozen section was performed as the first

TABLE 4.—*Survival Rate for Adenocarcinoma of Parotid Gland Treated by Radical Surgical Resection and X-Ray Therapy*

	Total	Died 1-3 Years	3 Year Survival	5 Year Survival	5 Year Cure
Number of cases	7	2	1	3	1
Percentage	..	29%	14%	43%	14%

step of the procedure. If this section showed malignant changes, the biopsy instruments were discarded and a wide removal of the entire parotid gland including the facial nerve performed, together with a radical neck dissection in most instances. The procedure was carried out through a vertical incision extending down the cheek and the lateral aspect of the neck to the clavicle, as performed by Dr. R. F. Bowers.[13] No attempt should be made to preserve the facial nerve. If there was any adherence of the tumor to skin, an ellipse of involved skin was removed with the tumor. The operation was aided by ligation of the external carotid artery before removal of the parotid was undertaken. Operation in these cases was followed by deep x-ray therapy. Results of the procedure are shown in table 4. One patient died of heart disease after three years without evidence of recurrence. Two, although alive after five years, show evidence of recurrence. One is alive and well five years after operation.

SUMMARY

Twenty-seven cases of mixed tumor and seven of adenocarcinoma of the parotid gland are presented. Twenty-seven of the 34 were followed for more than five years. Two mixed tumors recurred, and there has been one instance of total paralysis of the seventh nerve and four instances of partial paralysis. Operative techniques are discussed. Forty-five per cent of the patients with adenocarcinoma have survived for five years and 15 per cent have lived for five years without evidence of recurrence after radical operations and deep x-ray therapy.

13. Bowers, R. F.: Personal communication to the author.

CEREBROVASCULAR ACCIDENTS

Surgical Management with Particular Reference to Massive Intracranial Hemorrhage

E. S. GURDJIAN, M.D.
AND
J. E. WEBSTER, M.D.
DETROIT

CEREBROVASCULAR disease ranks third as a cause for death in the United States. In 1949, 340,000 victims died of cerebrovascular accidents. This tremendous mortality does not indicate the morbidity of the disease, since many times this number were partially and totally disabled.

The manifestations of cerebrovascular disease have been described for centuries. Cerebral hemorrhage was early and clearly recognized, while embolism and thrombosis were not known until the early part of the nineteenth century. The concept that hemorrhage in the brain disturbs the normal flow of animal spirits into the organs of sense and motion resulting in hemiplegia and unconsciousness was a theory inherited from Galen [1] in the second century. Wepfer,[2] in 1658, gave an excellent description of hemorrhage in the brain in his book on apoplexia. He also described accurately the blood vessels at the base of the brain, two decades later called the circle of Willis. Although aneurysm is mentioned in the works of Aetius [3] in the sixth century, the term arteriovenous aneurysm was apparently coined by William Hunter [4] in the eighteenth century. Aneurysms in the head and brain are mentioned only as possibilities prior to the nineteenth century. In the early part of the nineteenth century, many descriptions of aneurysms of the base of the skull and brain exist, with careful neurologic data.[5] Coe and Swayne [6] were the first to ligate the carotid artery in the neck for intracranial extradural aneurysm with success, in 1855. Moniz [7] in 1927 described the technique of angiography. The importance of this procedure in the diagnosis and management of cerebrovascular

Aided by a grant from the Kresge Fund.

From the Department of Surgery, Wayne University, and the Department of Neuro-Surgery, Grace Hospital.

1. Galen, cited by Mettler, C. C.: History of Medicine, Philadelphia, The Blakiston Company, 1947.

2. Donly, J. E., and Wepfer, J. J.: A Renaissance Student of Apoplexy, Bull. Johns Hopkins Hosp. **20**:1-9, 1909.

3. Aetius, cited by Erichsen, J. E.: Observations on Aneurism, London, The Sydenham Society, 1844.

4. Hunter, W., cited by Erichsen.[3]

5. Stumpff, A. A.: Pressure on Nerves and Pressure on Brain by Aneurysms, Am. J. M. Sc. **4**:35, 1836. Chevalier, T. W.: Case of Aneurysmal Tumor Between the Brain and Sella Turcica, ibid. **2**:203-204, 1828.

6. Coe and Swayne, cited by Mettler.[1]

7. Moniz, E.: L'encéphalographie artérielle, son importance dans la localisation des tumeurs cérébrales, Rev. neurol. **2**:72-90, 1927.

disease cannot be overemphasized. A monograph by Dandy [8] (1944) on intracranial aneurysms has founded a surgical concept of treatment. Anticoagulant therapy, which has been successful in cardiovascular disease also, is being used for patients who have cerebrovascular disease. Cervical sympathetic block was discussed and suggested by Leriche [9] in 1934 and revived by Gilbert and DeTakats [10] in 1948.

The surgical treatment of massive intracranial hemorrhage has been considered in the papers of Cushing,[11] Russell and Sargent,[12] Kron,[13] Bagley,[14] Penfield,[15] Craig and Adson,[16] Pilcher,[17] Furlow and Carr,[18] Rowbotham and Ogilvie,[19] Scott,[20] Hamby,[21] David and Hecaen,[22] Guillaume and Joinville,[23] Grant,[24] Gurdjian and Webster [25] and others. In the greatest majority the mass lesion was in the temporoparietal area on one or the other side. There have been a few cerebellar hematomas in the group. Angiography was not used in the evaluation of such cases except in one study (Gurdjian and Webster [26]).

8. Dandy, W. E.: Intracranial Arterial Aneurysms, Ithaca, N. Y., Comstock Publishing Company, Inc., 1944.

9. Leriche, R., and Fontaine, R.: L'anesthésie isolé du ganglion étoilé: sa technique, ses indications, ses résultats, Presse méd. **42**:849-850, 1934.

10. Gilbert, N. C., and deTakats, G.: Emergency Treatment of Apoplexy, J. A. M. A. **136**:659-665 (March 6) 1948.

11. Cushing, H.: The Blood Pressure Reaction of Acute Cerebral Compression, Illustrated by Cases of Intracranial Hemorrhage: A Sequel to the Mütter Lecture for 1901, Am. J. M. Sc. **125**:1017-1044, 1903.

12. Russell, A. E., and Sargent, P.: Apoplectiform Cerebral Haemorrhage: Operation; Evacuation of Blood; Slow Improvement, Proc. Roy. Soc. Med. **2**:44-52, 1908-1909.

13. Kron, I., and Mintz, W. G.: Kleinhirnblutung, geheilt durch Operation, Deutsche med. Wchnschr. **53**:1054, 1927.

14. Bagley, C., Jr.: Spontaneous Cerebral Hemorrhage: Discussion of 4 Types, with Surgical Considerations, Arch. Neurol. & Psychiat. **27**:1133-1174 (May) 1932.

15. Penfield, W.: The Operative Treatment of Spontaneous Intracerebral Hemorrhage, Canad. M. A. J. **28**:369-372, 1933.

16. Craig, W. M., and Adson, A. W.: Spontaneous Intracerebral Hemorrhage: Etiology and Surgical Treatment, with Report of 9 Cases, Arch. Neurol. & Psychiat. **35**:701-716 (April) 1936.

17. Pilcher, C.: Subcortical Hematoma: Surgical Treatment, with Report of 8 Cases, Arch. Neurol. & Psychiat. **46**:416-430 (Sept.) 1941.

18. Furlow, L. T.; Carr, A. D., and Wattenberg, C.: Spontaneous Cerebral Hemorrhage: Surgical Treatment of Selected Cases, Surgery **9**:758-770, 1941.

19. Rowbotham, G. F., and Ogilvie, A. G.: Chronic Intracerebral Haematomata: Their Pathology, Diagnosis, and Treatment, Brit. M. J. **1**:146-149, 1945.

20. Scott, M.: Surgical Treatment of Spontaneous Nontraumatic [Intracerebral] Hematomas [of Left Temporal Lobe], J. A. M. A. **130**:845-850 (March 30) 1946.

21. Hamby, W. B.: Gross Intracerebral Hematomas: Report of 16 Surgically Treated Cases, New York J. Med. **45**:866-876, 1945.

22. David, M., and Hecaen, H.: Nouvelle contribution à l'étude clinique et thérapeutique des hématomes intra-cérébraux spontanés, Presse méd. **53**:371-372, 1945.

23. Guillaume J., and Joinville, R.: Les hématomes spontanés intracérébraux, Presse méd. **53**:606-607, 1945.

24. Grant, F. C., and Austin, G. M.: Intracerebral Hemorrhage, with a Report of 14 Surgically Treated Cases, Tr. Am. Neurol. A. **73**:24-28, 1948.

25. Gurdjian, E. S., and Webster, J. E.: Neurosurgical Aspects of Cerebro-Vascular Accidents, 4th Congress Neurologique, Paris, Masson et Cie, 1949.

26. Gurdjian, E. S., and Webster, J. E.: Surgical Management of Cerebro-Vascular Disease, Tr. Am. Neurol. A., 1950, vol. 75.

Eleven Operative Cases of Spontaneous Intracerebral Hemorrhage

Name and Date	Age and Sex	Onset of Symptoms and Signs	Spinal Fluid	Focal Signs	Roentgen Findings, Survey of Skull, Angiograms and Air Studies	Operative Data	Result and Final Diagnosis
W. S. 9/21/48	21 M	Sudden onset of vomiting, severe headaches, unconsciousness 2 days before admission; left-sided weakness	Grossly bloody Initial pressure, 240 mm. of water	Nuchal rigidity, stuporous, left-sided pyramidal tract signs	Survey x-rays: negative Angiogram: localized extravasation in frontoparietal area on the right side, due to presence of a hemangioma, 9/23/48	9/25/48: 1½ oz. (45 Gm.) of intracerebral clot removed from right frontal lobe through a small trephine opening 10/11/48: osteoplastic craniotomy; excision of anomalous vessels of the cortex immediately over the area of hemorrhage; exploration of the area of hemorrhage which now consists of a cavity with clear fluid with smooth necrotic lining	Improved; ruptured hemangiomatous tissue; intracerebral hemorrhage, right frontal massive
B. H. 3/26/49	28 F	Known hypertension; numbness and paralysis of the right half of the body developed the night before admission	Xanthochromic Initial pressure, 450 mm. of water	Right-sided pyramidal tract signs with papilledema on the left side	Angiogram: a large cavity, where clot was removed and patent vessels in the distribution of the middle cerebral group, 5/20/49	5/18/49: left parietal lobe trephined, with removal of 20 cc. of blackish fluid followed by injection of diodrast* into the cavity; clot reaspirated through the same opening five days later with about 15 cc. of fluid obtained	Improved; intracerebral hematoma, left parietal
P. R. 3/31/49	50 M	"Stroke" 5 weeks before with left-sided paralysis; improving but continued to have increasing headaches	Clear Initial pressure, 190 mm. of water	Choked disks; left homonymous hemianopsia; left lower facial weakness	Skull: normal Ventriculography: obliteration of right temporal horn and displacement of the ventricles to the left, 4/4/49	4/7/49: right temporoparietal osteoplastic craniotomy; removal of intracerebral clot from right temporoparietal area	Improved; intracerebral hemorrhage, right temporoparietal region
J. K. 6/7/49	30 M	Attack of unconsciousness, with right hemiplegia and motor aphasia in October 1946 with recovery; recurrence of hemiplegia and aphasia about 3 weeks before admission	Xanthochromic Initial pressure, 260 mm. of water	Right hemiplegia; Jacksonian convulsions, motor aphasia	Survey x-rays: negative Angiogram: hemangioma of the left anterior parietal area, 6/10/49 Encephalogram: midline shift of the ventricular system of cavities to the left, 6/21/49 Arteriogram: postoperative Angiomatous lesion somewhat smaller, 8/12/49 Arteriogram: Angiomatous lesion smaller but persists, 3/16/50 Arteriogram: postoperatively angiomatous lesion completely gone, 4/5/50	6/28/49: removal of intracerebral clot in left parietal area; cautery of aneurysmal vessels 3/18/50: osteoplastic craniotomy; excision of aneurysmal tissue; tying of the aneurysmal vessels with silver clips and cautery	Continued hemiparesis and partial motor aphasia and Jacksonian seizures up to the present time; angioma right frontoparietal, left frontal hematoma
J. S. 6/24/49	56 M	Coronary episode 6 years before; known hypertension; sudden onset of unconsciousness with left hemiplegia on night before admission	Bloody fluid Initial pressure, 325 mm. of water	Left hemiplegia; bilateral papilledema; later left homonymous hemianopsia	Survey x-rays: negative Angiogram: anterior cerebral markedly shifted toward the left, 7/5/49	7/8/49: trephinement, right temporoparietal area, just above and behind the right ear; 2½ oz. (75 Gm.) of tarry, fluid blood clot removed with small black clots in suspension; cavity visualized with diodrast*	Improved; paralysis of the left half of the body continued for nine months; right temporoparietal cerebral hemorrhage

J. P. 6/27/49	30 M	Sudden onset of vertigo and headaches with right hemiplegia 6 days before admission	Bloody fluid Initial pressure, 350 mm. of water	Right hemiplegia; speech hesitant, but remarkably good	Survey x-rays: negative Angiogram: unusual network of blood vessels in posterior parietal region near the midline on the left side, 6/30/49	7/6/49: intracerebral hematoma, left posterior parietal area near the midline; about 30 cc. of old fluid clot removed	Improved; cerebral hemorrhage, parieto-occipital, subcortical on the left side
M. L. 11/30/49	59 F	Known hypertension for several years; collapsed on day of admission, 11/30/49	Bloody fluid Initial pressure, 360 mm. of water	Paralysis of the right side of the body and aphasia; semiconscious state	Survey x-rays: not helpful Angiogram: middle cerebral extravasation of small amounts of dye; anterior cerebral shifted to the right, 12/7/49	12/8/49: left subtemporal decompression; subdural hematoma removed; cerebral hematoma, temporal area also aspirated	Died 12/19/49; no autopsy; temporoparietal intracerebral hematoma and left subdural hematoma
M. O. 12/3/49	39 F	History of frequent headaches for 13 years; hemiparesis of the left side of 6 days' duration; severe headaches and semiconsciousness	Bloody fluid Initial pressure, 190 mm. of water	Left hemiparesis; left astereognosis	Survey x-rays: negative Angiogram: essentially normal records, 12/5/49	12/4/49, 12/5/49, 12/6/49: posteroparietal trephinement on the right side, with removal of 50 cc. of blood each time 12/6/49: osteoplastic craniotomy of right parietal area; area of hemorrhage explored and bleeding points packed	Died 12/7/49; autopsy revealed no unusual vasculature
R. W. 3/2/50	21 M	"Nervousness" for 3 years; subarachnoid hemorrhage one week prior to admission	Clear fluid Initial pressure, 400 mm. of water	Right-sided headaches; left homonymous hemianopsia	Skull: pineal body shifted to left Angiogram: middle cerebral group of vessels displaced forward and upward, 3/6/50 Air study not done	3/9/50: right parietotemporal osteoplastic craniotomy; intracerebral clot in temporo-parieto-occipital junction, right side	Improved; right temporoparietal intracerebral hemorrhage
H. Z. 4/12/50	54 M	Sudden onset of dizziness, vomiting, jargon speech, 2 weeks before admission; right-sided weakness	Xanthochromic Initial pressure, 400 mm. of water	Right-sided weakness with choked disks and jargon speech; hypertension; left homonymous hemianopsia	Survey x-rays: negative Angiogram: essentially negative 4/19/50 Encephalogram: left lateral ventricle slightly depressed and pushed over toward the right, 4/17/50	4/21/50: trephinement of left parieto-occipital area; large intracerebral hematoma of the parieto-occipital region removed; 30 cc. of wine-colored material evacuated; cavity visualized with diodrast*	Improved; cerebral hemorrhage, massive, parieto-occipital region
C. P. 6/22/50	50 M	Sudden onset of nausea followed by unconsciousness, with right hemiplegia 3 days before admission	Xanthochromic Initial pressure, 400 mm. of water	Right hemiplegia and aphasia	Survey x-rays: negative Arteriogram: sylvian vessels elevated on the left, 6/26/50 Encephalogram: slight shift of ventricles to the right and posterior portion of lateral horn of the left ventricle compressed, 7/3/50	7/6/50: trephinement over parietotemporal region on the left side with removal of 40 cc. of fluid clot; visualization of the cavity with diodrast*	Improved; intracerebral clot, left parietotemporal

* Registered trademark.

The present paper is an analysis of 11 patients with massive intracranial hemorrhage treated by surgery from a group of 50 patients with cerebrovascular disease and sudden hemiplegia or hemiparesis. All but one were studied by angiography. In some cases, air studies and direct visualization of the lesion by contrast mediums were also utilized. These patients were treated during a 21 month period from September 1948 to June 1950.

MATERIAL

In the accompanying table a résumé of the cases and the treatment is given.

Sex and Age.—Eight among the eleven patients were male; five were under the age of 40 and six were over 50 years. The oldest patient in the group was 59 and the youngest 21. Among the younger group there were two patients with arteriovenous malformation resulting in massive hemorrhage, and one was known to have hypertension. Among those over 50 years of age, four of the six patients were known to have hypertension. A sudden attack of hemiplegia in a young person is an indication for careful evaluation of its etiology.

Onset of Symptoms and Signs.—A sudden attack of giddiness and/or vomiting was the initial symptom in four cases. Unconsciousness supervened in eight cases. There was hemiplegia or hemiparesis in all the patients. In patient P. R. hemiplegia involving the left side improved. Homonymous hemianopsia affecting the left side was noted as the patient became more cooperative. With returning consciousness, he complained of severe headaches. About four weeks after the "stroke" the patient was able to walk. Examination of fundi then showed papilledema. A right temporoparietal massive clot was evacuated (fig. 1).

Spinal Fluid.—The spinal fluid was bloody in all but one case. The spinal fluid pressure was high in the greatest majority, being over 300 mm. of water in seven cases. In three patients the pressure ranged from 190 to 260 mm. In patient P. R. there was clear spinal fluid, with a pressure of 120 mm. of water. Initially, this patient was considered to have a cerebral thrombosis, and he was treated by means of stellate blocks and anticoagulant therapy. At the end of four weeks a massive hemorrhage was diagnosed on the basis of the occurrence of papilledema with severe headaches. A massive hemorrhage was found in the right temporoparietal region.

The diagnosis of cerebral hemorrhage in the absence of bloody spinal fluid is difficult. Clear spinal fluid with low pressure in a patient with hemiplegia, unassociated with unconsciousness, favors the diagnosis of cerebral thrombosis. However, as in the case above, the spinal fluid pressure may be low and the fluid clear, yet there may be a surgical type of hematoma in the cranial cavity. In patient P. R. the possibility of secondary hemorrhage from the anticoagulant therapy was thought to be unlikely, since the prothrombin time was never under 25 per cent of normal.

X-Ray Findings.—Survey studies of the skull showed no abnormalities except, in one instance, a mild shift of the pineal body. Ten among the 11 patients reported in this paper had angiographic study of the affected carotid circulation. The angiogram lateralized the lesion in seven cases (figs. 3, 4). In two an angiomatous lesion was located (W. S. and J. K., figs. 5, 6). The angiogram on patient H. Z. was normal, but the air encephalogram showed a shifting of the left lateral ventricle to the right with a slight depression of the posterior portion of the

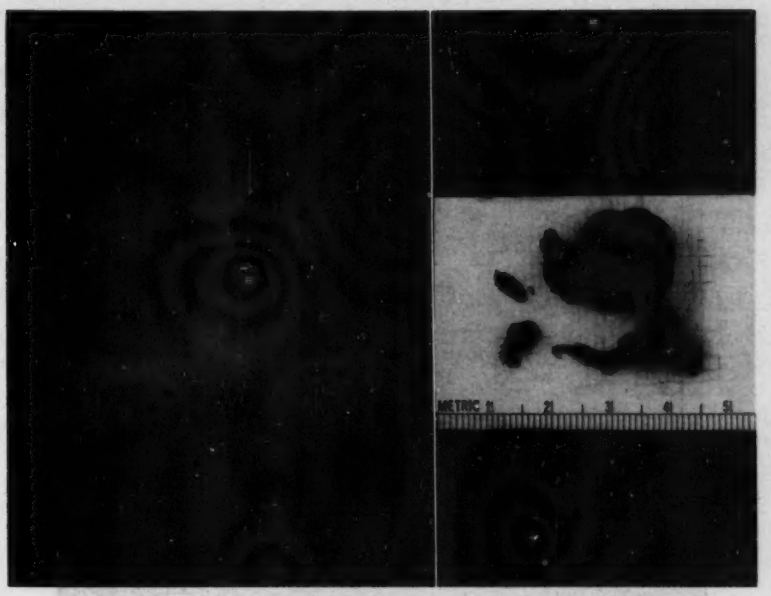


Fig. 1.—Ventriculogram on P. R. and a portion of the clot removed from right temporal region.

Fig. 2.—Encephalogram on H. Z. showing a shift of the ventricles to the right and an outline of the cavity containing the clot visualized with diodrast® injected into the lesion. The cavity of the clot communicated with the ventricles as shown by simultaneous visualization of the clot cavity and the ventricles. Angiograms were essentially normal. The fluid clot is shown in the test tubes.

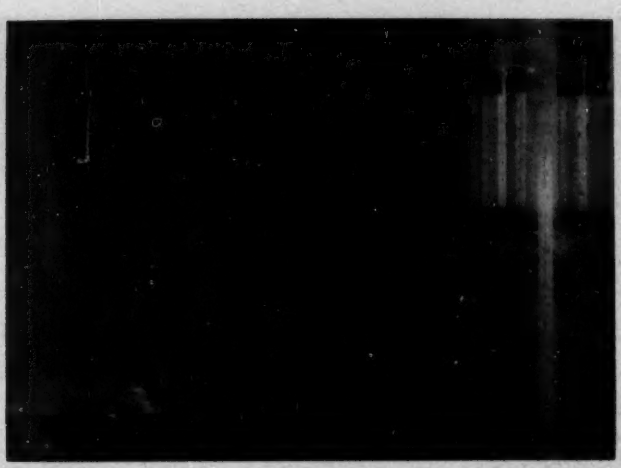


Fig. 3.—Extravasation of diodrast® into the clot cavity (I. P.). Trephine in the left parieto-occipital region permitted the evacuation of the clot shown in the test tubes.

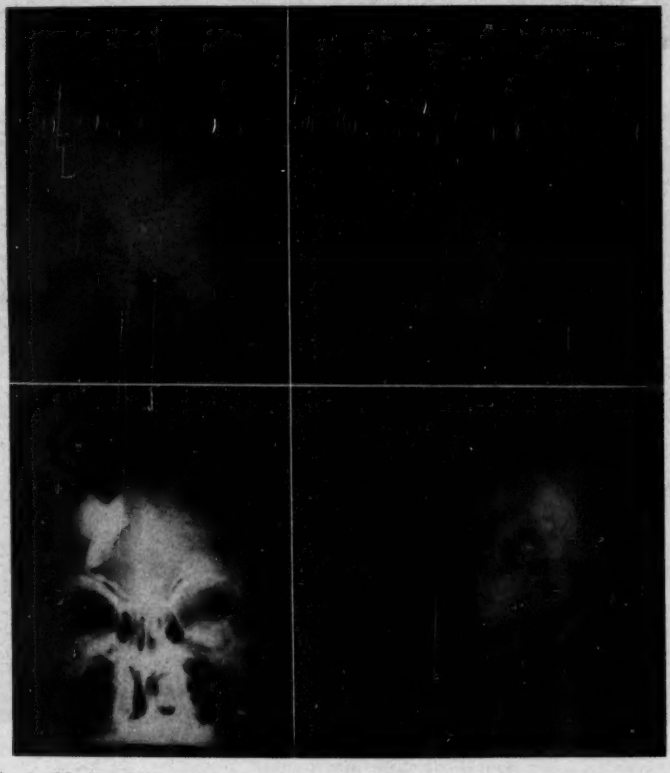


Fig. 4.—Marked shifting of the anterior cerebral artery in I. S. The cavity of the clot in the right temporoparietal region is visualized with diodrast.®

Fig. 5.—Angioma of left frontal area with large clot in J. K., with depression of the sylvian vessels. Osteoplastic craniotomy for removal of the clot and attempt at obliteration of the angioma. Postoperative angiograms revealed angioma still patent. A second craniotomy for excision of angioma was successful, as shown by final angiograms with complete disappearance of the lesion.

Fig. 6.—Angiogram on W. S. showing an angioma of the right frontal lobe. One and a half ounce (45 Gm.) fluid clot was removed through a trephine opening in the right frontal area. Two and a half weeks later the angioma was excised through an osteoplastic flap. Angiomatous mass is shown injected with diodrast® after excision.

ventricle (fig. 2). In this instance, there was no shift of the anterior cerebral vessels in the anteroposterior view. Supratentorial lesions in the more forward areas of the brain are well lateralized by angiography. In cases of supratentorial lesions in the posterior third of the head, angiographic findings may be misleading; air studies have been more accurate in lateralizing the mass. In one patient, P. R., only air studies were used to locate the lesion (fig. 1).

In the greatest majority of the patients, angiography was carried out two or more days after the onset of the disease. If the patient's condition is poor, it may be advantageous to delay making the angiogram. With localizing signs present, if there are evidences of increased intracranial pressure, trephine exploration may be carried out before angiography is employed. This was done in three of the 11 patients in this series. As the patient improves, angiography should be carried out to determine the type of lesion responsible for the hemorrhage. In patient W. S. an angiomatous lesion was thus found, after the patient was past the critical phase following the evacuation of a frontal lobe hematoma.

Focal Signs.—Right hemiparesis or hemiplegia was present in six cases, and left hemiparesis or hemiplegia was seen in five. Pyramidal tract signs accompanied the deficits. Papilledema occurred in three. A homonymous hemianopsia on the left side was present in four cases; right homonymous hemianopsia was noted in two.

Operative Findings.—In many instances, the massive hematoma was liquid and easily accessible to a blunt ventricular needle for evacuation by aspiration. A collection in the temporoparieto-occipital area was seen in seven patients (figs. 2, 4). There were two frontal lobe hematomas and two located in the parieto-occipital area.

A parietotemporo-occipital hematoma is reached through a trephine opening an inch (2.5 cm.) above and a little behind the ear. The needle is introduced medially and somewhat forward toward the temporal lobe. A liquid hematoma may flow through the ventricular needle. More may be aspirated with a syringe. The cavity is washed out with saline, and reaspiration of the saline and the remaining clots may be carried out several times. In four of the 11 cases the extent of the hemorrhage in the cranial cavity was ascertained by injecting iodopyracet solution U. S. P. (diodrast®) into the cavity after partial evacuation of the clot. Aspiration through a trephine opening was used in six cases. In two others, initially, a trephine hole was used, followed by osteoplastic craniotomy for removal of an angioma in one instance and to control hemorrhage in the other. In one patient a subtemporal decompression was utilized. In four an appropriate osteoplastic craniotomy was used to remove the clot after transcortical incision.

COMMENT

The following steps are important in the management of the patient with a cerebrovascular accident:

1. An accurate history of the present illness and past events pertinent to the patient's condition should be elicited.

2. Neurologic examination for the localization of the lesion, roentgen studies of the skull and an electroencephalogram should be made.

3. A lumbar puncture is necessary, with recording of the spinal fluid pressure and examination of the fluid for blood content, cell count, total protein and serologic data.

4. If the disability remains constant for 24 hours on conservative treatment and if the patient's condition permits, angiography is used to identify the type and position of the lesion (percutaneous angiographic technique with local infiltration or with thiopental sodium anesthesia).

5. If a diagnosis of cerebral thrombosis is certain, repeated stellate blocks may be used.

6. If a massive intracerebral hemorrhage is identified, evacuation by trephine may be first attempted. The instillation of diodrast® or thorotrast® (thorium dioxide preparation) may outline the extent of the collection.

7. If signs of increasing intracranial pressure continue or if evacuation by trephine is not adequate, removal of the lesion by appropriate exposure through craniotomy may be necessary.

8. The surgical removal of a lesion which may cause a repetition of the bleeding is worth while.

9. Rehabilitation should be begun as soon as possible in the hospital.

It is obvious that many patients with cerebrovascular disease need not undergo the management outlined above. A single short period of weakness or numbness in one half of the body or a period of aphasia, followed by normal activity within a matter of hours, is obviously not the type of symptom complex deserving this regimen. If the patient has repetitions of focal symptoms and signs, one then may advise special studies.

The examination of the spinal fluid is important in this class of patient. The presence of blood in the spinal fluid and the pressure of the spinal fluid should be determined. A clear spinal fluid with low pressure would favor the diagnosis of cerebral thrombosis. A massive clot, on the other hand, is usually associated with an increased spinal fluid pressure. Occasionally, a patient with clear spinal fluid may have a massive clot. The presence of bloody spinal fluid makes further studies desirable to determine the origin of the bleeding.

Signs of compression may become manifest soon after a cerebrovascular accident. Occasionally, the patient may temporarily improve and then later manifest signs of increased intracranial pressure (R. W.).

In the presence of signs of compression (headaches, increasing stupor, lowering pulse and respiratory rate, increasing blood pressure), exploration may be indicated. It may be safer to explore through a trephine opening, evacuate the collection and thus relieve the increasing intracranial pressure. Angiography may be done later to determine the origin of the bleeding.

Angiography is a simple procedure and an important step in management. A 35 per cent solution of diodrast® has not been dangerous in our hands. In the older person, thorotrast® may be used with safety. When diodrast® is used, patients are tested for diodrast® sensitivity. Angiography can be carried out percutaneously with either local or thiopental sodium anesthesia. We have not used stellate blocks in patients who undergo this procedure. If angiography and/or air studies reveal the presence of a mass, causing a shifting of the vessels or the ventricular system, such a lesion must be removed. Occasionally, there may be a shifting of the ventricles with normal angiographic delineation. This is particularly true with occipital masses.

The pathologic lesion in many patients with massive intracranial hemorrhage is a semiliquid collection with necrotic brain tissue constituting the lining of the wall of the mass. This lining of softened necrotic brain tissue may become mixed with the semiliquid collection. Visualization of the lesion is possible by injecting diodrast® or thorotrast® into the cavity of the collection following aspiration or removal of the contents. In some cases, there may be clotted material in the lining of the wall, with liquid and semiliquid hemolyzed material toward the center of the cavity. The collection is usually located in the temporoparieto-occipital area, as shown in figures 2 and 4 (Craig and Adson,[16] Hamby,[21] Scott,[20] Guillaume and Joinville,[23] and others). If the patient has homonymous hemianopsia, in addition to the hemiparesis or hemiplegia, such a location is most likely. A trephine opening placed 1 inch (2.5 cm.) superior and ½ inch (1.3 cm.) posterior to the ear will permit introduction of a blunt needle into the collection (David and Hecaen [22]). If no collection is noted or if the patient does not seem to improve on repeated aspiration of the collection, then an appropriate craniotomy to expose the area of the mass lesion is indicated. The collection is then removed through a transcortical incision. Collections which cause a shifting of the ventricles or the vascular system have to be rather large. In many instances they have been over 30 cc. in size. If such a mass can cause sufficient pressure to distort the vascular pattern or the ventricles, its removal is beneficial. This has been proved by clinical experience.

Operative intervention to excise the lesion which may cause a repetition of the bleeding is a question which has to be decided on after thorough study of the individual case.[27] Excision of the lesion by a procedure which may result in death or profound disability is an error of surgical judgment to be avoided. However, since a repetition of the bleeding may be fatal, careful thought should be given to the possibility of treatment.

Rehabilitation of the patient with cerebrovascular disease is not within the scope of this paper, but its importance in management deserves emphasis in any discussion on this subject. In a recent paper, Newman [28] and Rusk [29] discussed the rehabilitation of this class of patient.

SUMMARY AND CONCLUSIONS

Eleven patients with large hemorrhagic collections due to cerebrovascular disease who were operated on have been reported.

Angiography is most helpful in locating such masses and in estimating their size. It may aid in determining the lesion responsible for the hemorrhage.

Surgical treatment of hemorrhagic collections due to cerebrovascular disease is possible through a small opening over the site of the hemorrhage. Drainage of the collection by aspiration through a trephine opening was satisfactory in six cases. A larger exposure was required in the other five cases.

---

27. Norlen, G.: Arteriovenous Aneurysms of the Brain: Report of 10 Cases of Total Removal of Lesions, J. Neurosurg. **6**:475-494, 1949. Olivecrona, H., and Riives, J.: Arteriovenous Aneurysms of the Brain: Their Diagnosis and Treatment, Arch. Neurol. & Psychiat. **59**:567-602 (May) 1948.

28. Newman, M. K., and Cohen, L.: Physical Medicine and Rehabilitation in the Management of Hemiplegia in the Adult, J. Michigan M. Soc. **49**:917-922, 1950.

29. Rusk, H. A.: The Internist's Number 1 Problem—Chronic Disease in an Aging Population, Ann. Int. Med. **33**:1341-1348, 1950.

DISCUSSION

Dr. Howard C. Naffziger, San Francisco: The interest and the development of knowledge with reference to circulatory disturbances in the brain are certainly the big, important step in recent years in neurological diagnosis and in surgical therapy. It makes one realize that without the assistance gained from the roentgenologists over the last 20 or 30 years we would not have got far in the diagnosis of either spinal or intracranial conditions. Our concepts of diagnosis are undergoing revision, and certain diagnostic patterns are beginning to emerge.

The problem discussed today is different from that of the elderly person in whom hemiparesis came on at night when he was quiet and his blood pressure was presumably low. Such persons are still the ones who perhaps would benefit most from anticoagulant therapy and from injections in sympathetic ganglions. The patients whom Dr. Gurdjian is discussing are young. Juvenile hemiplegia is the cerebral disturbance which occurs in young persons and in those in the active period of their lives.

I should like to ask Dr. Gurdjian if he could not give us the age presentation in a little different way, because I think that would help to establish in our minds certain diagnostic patterns. He has given us the ages of the patients by decades, corresponding with the appearance of hemiplegia with unconsciousness or semiconsciousness, and then the ages of those who have come in with bloody fluid. I think that if the ages were given opposite the type of lesion found, they would help us to establish some of these patterns. I should also like to ask Dr. Gurdjian whether he has any thoughts as to the particular mechanism by which the thromboses in the common and internal carotid artery (which we have also seen) were brought about.

I have been interested in the relatively small proportion of arteriovenous anomalies in his series. We have had a much higher proportion; they are all very large and practically always involve the motor area and frequently areas related to speech. From a surgical standpoint, we find altogether too many which extend down in the midline and are relatively inaccessible. However, even patients with involvement of the motor area have done surprisingly well, judged by the expectations and fears which one had before operation. They have had much less of a neurological deficit than would be anticipated. I believe that Dr. Gurdjian will come to feel that even some of these large anomalies in the motor area, which seem to have deep arterial connections, can be attacked surgically.

This is the proper place to stress the desirability of early angiography. We have been timid about angiography in persons who had had recent bleeding, fearing that the injection of about 35 cc. of material into the carotid artery would blow out a clot or promote bleeding. However, it has been perfectly well established that the injection of that material does not raise the pressure in the carotid beyond the point of injection, so that fear can be discounted.

Our catastrophes have resulted, in early times, from saying, "Well, we had better wait for one or two or three weeks, or send the patient home and have him come back in a month." I am confident now that this policy is a mistake and that we lose more patients by deferring angiography than by doing it early and will often miss those patients who might be best treated surgically.

Dr. John E. Adams, San Francisco: As pointed out by the previous speakers, certainly one of the striking aspects in the development of neurological surgery in the last decade has been the tremendous development in the attack on cerebrovascular diseases. Dr. Gurdjian and Dr. Webster are to be congratulated on their energetic approach to this problem and on their interesting presentation. Our experience with both angiomas and aneurysms bears out the contention that they carry high morbidity and mortality rates if left alone. Certainly, the answer to this problem is a more radical approach, such as has been presented this morning.

So far as the treatment of acute cerebrovascular thrombosis and embolism is concerned, we have been interested in this problem for about three years. It is hard to assess this group of patients, in view of the fact that control is difficult and we do not know what would happen to the patients if they were not treated. However, we feel rather definitely that approximately one half of such patients have been benefited by repeated procaine blocks of the stellate ganglion. It is difficult to account for this success on the basis of the accepted physiology of the cerebrovascular circulation, since all the experimental work done in the past has indicated that the sympathetic nervous system has a definite but only slight effect on the caliber of the vessels in the brain. Furthermore, the role which vasospasm plays not only in the pathogenesis but also

in the continued picture in such patients is not fully understood. I believe, however, that in many instances spasm is present, and marked benefit can be expected by interruption of sympathetic impulses.

We have some experimental evidence on this point. To date, we have not been able to show any consistent effect of sympathetic block with procaine on the total cerebral blood flow, as measured by the nitrous oxide method of Kety and Schmidt. That there may be a transient effect on the total cerebral blood flow is suggested by measurements of spinal fluid pressure after blocking one or both stellate ganglions. If one places a needle in the lumbar canal and, after the establishment of a constant pressure, blocks the stellate ganglion, a transient rise in the spinal fluid pressure occurs, lasting from 30 to 40 seconds; the pressure then falls to its previous level. We think this occurrence probably indicates a transient increase of the amount of blood entering the cranial cavity, with almost immediate adjustment of the dynamics.

We have had three instances of subdural hematomas in which at operation, after evacuation of the clots, there was failure of expansion of the brain. After bilateral stellate block in each instance there was prompt response; the brain expanded to its normal position and resumed its normal pulsation.

Finally, by using a colloid preparation of radioactive yttrium, we have been able to demonstrate fairly conclusively in human beings that after a stellate block there is a rise in the vascularity of the ipsilateral cerebral cortex of approximately 15 to 20 per cent. There is some effect on the contralateral side, but the effect is largely ipsilateral. This rise has been consistent in 10 experiments.

I entirely agree with Dr. Gurdjian and Dr. Webster that there is a great deal of need for further research on this important problem.

DR. A. E. BENNETT, Berkeley, Calif.: I should like to ask Dr. Gurdjian what he has found out about the incidence of epilepsy in his follow-up of cases in which clots were aspirated. Is it as high as with brain abscess? In a number of cases I have been unhappy about the epileptic seizures which came on within three months to a year after the clots were aspirated.

DR. E. S. GURDJIAN, Detroit: In regard to the questions raised by Dr. Naffziger, I may say that arteriovenous anomalies of the brain will probably be attacked with greater and greater vigor as we know more about their pathologic physiology. On the other hand, as he stated, there are many examples involving the entire thickness of the hemisphere in the motor area, particularly on the left side, which would probably be better left alone.

At times, one finds an arteriovenous anomaly or an angioma when not expected. For instance, only the other day a 16 year old girl was sent to us from the ophthalmology clinic, where a diagnosis of possible Lindau's disease had been made, whose arteriogram showed a huge angiomatous formation on the same side as the retinopathy, with no complaints whatsoever. The question arises of what we are supposed to do about such cases. These problems, of course, will be answered as time goes on.

As to the question of the mechanism of production of thrombosis of carotid arteries in the neck, I think a majority of the pathologists feel that such thrombosis usually starts at the bifurcation and that the atheromas present at the bifurcation are the basis for the occlusion. In those with complete occlusion of the common carotid artery there may be a cerebral deficit on the opposite side and an optic atrophy on the same side as the thrombosis. The presence of unilateral optic atrophy should make one consider the possibility of a thrombosis of the common carotid or internal carotid artery.

I was gratified to hear Dr. Naffziger say we should obtain angiograms on these patients early. Of course, there is a possibility that the diodrast® may cause a vascular spasm among patients who are already severely ill; increasing spasm in the vasculature may be serious, but fortunately we have not found any difficulty in that connection. It is possible that in some of the cases the use of a cervical block may also be of some help.

The comments made by Dr. Adams are pertinent, and his material on cerebral thrombosis is important. As he stated, many patients should be treated in many clinics, so that we shall have a statistically sound number of cases. It is easy to ascribe good results to procedures, rather than natural causes. Laboratory research may be very important in connection with sympathectomy and resulting changes in the size of cerebral blood vessels.

As concerns the comments by Dr. Bennett, I would say that among the ten surviving patients there is one case of epilepsy, with attacks occurring three or four times a year. This patient had an aspiration of the clot.

THE Broyles Optical Bronchoscope

FOR OPTICAL VISUALIZATION OF INACCESSIBLE PORTIONS OF THE TRACHEAL BRONCHIAL TREE

The Broyles Optical Bronchoscope consists of the following:

Foroblique* examining telescope, providing magnified image of lesions in direct view.

Right angle examining telescope, permitting clear, magnified image of upper lobe bronchus and subdivisions.

Retrograde examining telescope, giving retrospective view of lower portions of lesions of trachea.

Operating telescope, providing clear, magnified image directly at jaws of *Biopsy Forceps* or *Grasping Forceps.*

Bronchoscopic tubes are supplied in lumen sizes 3, 4, 5 and 6 mm., 30 cm. long and with 7, 8 and 9 mm. lumen, 40 cm. long. Each tube includes a separate interchangeable light carrier. Also included, is a set of anti-fogging attachments.

The Broyles Optical Bronchoscope is available as a complete unit; or the individual telescopes, forceps, tubes and other components may be obtained separately.

* MacCarthy Optical System

Write for full information

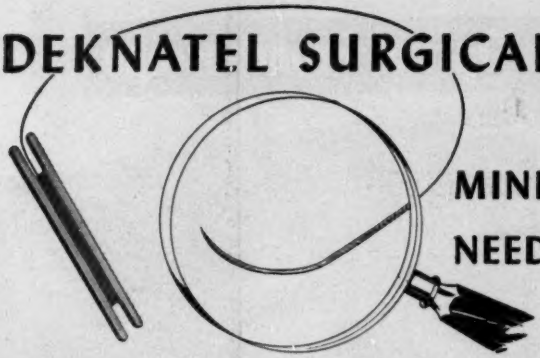
American Cystoscope Makers, Inc.

1241 LAFAYETTE AVENUE • FREDERICK A. WALLACE, PRESIDENT • NEW YORK 59, N. Y.

DEKNATEL SURGICAL SUTURES

with

MINIMAL-TRAUMA NEEDLES ATTACHED



Because of their uniform high quality, Deknatel sutures with Minimal-Trauma Needles attached are preferred by many surgeons for Eye, Vascular, Gastro-intestinal, Skin, Neuro, Plastic and other types of specialized surgery.

The needles are resilient, tempered, polished steel with sharp points and keen cutting edges. They are securely anchored to specified lengths of Deknatel Braided and Treated Surgical Silk—*the original moisture and serum resistant surgical silk suture.* A streamlined suturing combination to minimize perforation and trauma.

Deknatel

QUEENS VILLAGE S. (L. I.) NEW YORK

SUPPLEMENT to EXPERIENCE

A.M.A. Archives of INTERNAL MEDICINE

UNDER some circumstances, sometime in his career, practically every physician becomes an internist. Contact with forward-moving practices and opinions in the internal medicine field . . . provided in A. M. A. INTERNAL MEDICINE . . . supplies confirmation and supplements experience for both the specialist and the physician in general practice.

Featured each month will be comprehensive original articles, case reports, clinical studies, progress reports, correspondence, news and comment, book reviews.

Able editorial leadership.

Outstanding contributions.

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St., Chicago 10, Illinois.

Please Begin My Subscription to A. M. A. Archives of INTERNAL MEDICINE with the Next Issue.

.....M.D.

.....STREET

.....CITY & STATE

$10.00 YEARLY

$11.00 FOREIGN $10.40 CANADIAN

Dihydrostreptomycin Sulfate

a Drug of Choice

for Physician and Patient

Extremely well tolerated and rarely causing irritation on injection, Dihydrostreptomycin Sulfate has become a most widely accepted streptomycin preparation.

***Comparative studies by leading clinicians confirm that* DIHYDROSTREPTOMYCIN SULFATE IS—**

as effective as streptomycin [2, 9, 13-15]

less toxic for the vestibular apparatus [1-15]

minimizes pain and swelling at the site of injection [6, 10]

may be used even in patients showing allergic response to streptomycin [2, 9, 10, 11]

Extensive experimental studies [6, 9, 16-18] ***proved* CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK *less toxic for the vestibular system.***

BIBLIOGRAPHY

(1) Tompsett, R., and McDermott, W., Am. J. Med. *7*: 371-381, Sept. 1949. (2) Tompsett, R., Ann. Otol., Rhin. & Laryng. *57*: 181, March 1948. (3) Sweany, H. C., Dis. Chest *15*: 631-656, June 1949. (4) Lincoln, S., Science News Letter *55*: 307, May 14, 1949. (5) Semans, J. H., J. M. A. Georgia *39*: 477-480, Nov. 1949. (6) Donson, C. M., Kilbourne, P. C., and King, E. Q., Amer. Rev. Tuberc. *60*: 564, 575, Nov. 1949. (7) Nagley, M. M., Brit. M. J. *1*: 248, Jan. 28, 1950 (in correspondence). (8) Committee on Medical Research and Therapy, American Trudeau Society, Am. Rev. Tuberc. *61*: 436-440, March 1950. (9) Carr, D. T., Hinshaw, H. C., Pfuetze, K. H., and Brown, H. A., Dis. Chest *16*: 801-821, Dec. 1949. (10) Odell, J. M., Dis. Chest *16*: 818, Dec. 1949. (11) (Editorial) New England J. Med. *240*: 736, May 5, 1949. (12) Keefer, C. S., Ann. Int. Med. *33*: 582-589, Sept. 1950. (13) Marah, D. F., W. Va. Med. J. *45*: 280-284, Oct. 1949. (14) Johnson, H. M., J. Invest. Dermat. *15*: 61-66, July 1950. (15) Hinshaw, H. C., Personal communication. (16) Lincoln, N. S., Horton, R., Stokes, A. M., Monroe, J., and Higgins, H. M., Am. Rev. Tuberc. *62*: 572-581, Dec. 1950. (17) Carr, D. T., Brown, H. A., Hogson, C. H., and Heilman, F. R., J. A. M. A. *143*: 1223-1225, Aug. 5, 1950. (18) Jacoby, A., Goldberg, W., Sobel, N., and Rosenthal, T., Am. J. Syph., Gonor. & Ven. Dis. *34*: 185-186, March 1950.

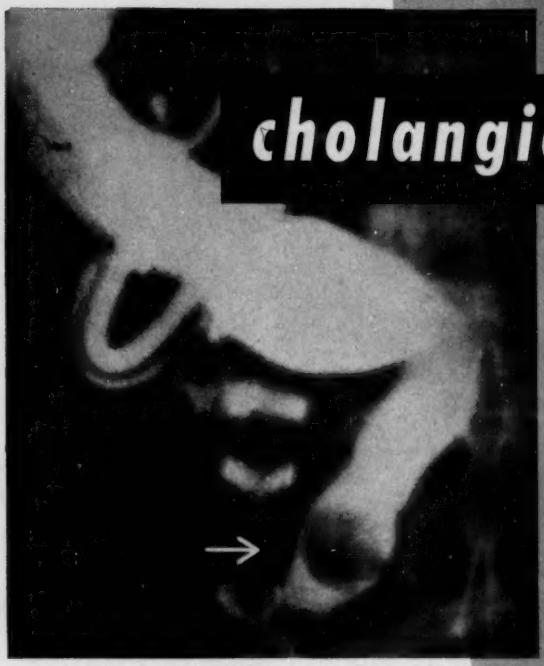
Supplied By Merck In The Purest Form Available—

CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK

Crystalline Dihydrostreptomycin Sulfate Merck is supplied in convenient 1 Gm. and 5 Gm. vials.

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

cholangiography



Cholangiogram with Diodrast 35% showing stone in distal end of common duct. Illustration, courtesy of Dr. J. Buckstein, author of "The Digestive Tract in Roentgenology" (Lippincott, 1948) in which a whole chapter is devoted to this procedure.

Easy Roentgenologic Detection of "the 10 to 18 per cent of stones left behind after common duct exploration"[1]

"Since 1934 we have employed visualizing cholangiograms in all operations on the extrahepatic biliary system. More than 1700 studies have been made and from this experience much information has been obtained. Operative cholangiograms demonstrate congenital aberrations and anatomic displacements of the extrahepatic biliary system; determine patency of the ductal system; note number and position of offending calculi; designate functional status of the sphincter of Oddi; outline fistulous communications; visualize bile reflux into the pancreatic ducts; detect intrusions of neoplasms which impinge on the large bile ducts or originate in the ampulla of Vater; and visualize dilatation, sacculation or diverticular enlargements of the bile ducts themselves. Such exact information permits the surgeon to select the operative procedures best suited to alleviate existing pathologic abnormalities."[2]

1. Byrne, R. V.: Amer. Jour. Surg., 78:514, Oct., 1949.
2. Hicken, N. F., Stevenson, U. L., Franz, B.J., Crowder, Earl: Amer. Jour. Surg., 78:347, Sept., 1949.

Diodrast®

35% SOLUTION

BRAND OF IODOPYRACET INJECTION

For Clear Visualization of the Biliary Tract

Also Urinary Tract, Arteries, Veins

Ampuls of 10, 20 and 30 cc.

Simplified Technic

For a detailed discussion of a simple fractional method for cholangiography postoperatively or operatively write for illustrated pamphlet.

Winthrop-Stearns INC.

NEW YORK 18, N. Y. WINDSOR, ONT.

Diodrast, trademark reg. U. S. & Canada